SYNTHESIS OF FUNCTIONAL (THIA)CALIX[4]ARENE DERIVATIVES USING MODULAR AZIDE – ALKYNE CYCLOADDITION APPROACH

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Abstract

Today, the modification of the organic molecules using the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) is of great interest, as evidenced by the Nobel Prize in Chemistry awarded in 2022 to the founder of “click” chemistry. Supramolecular chemistry, in turn, is one of the actively developing branches of modern science. Using the CuAAC approach is a very convenient method to obtain new macrocyclic structures of interest. This review focuses on the use of the modular “click”-chemistry approach for the synthesis of various triazole derivatives of thiacalix[4]arenes and calix[4]arenes as well as general routes for the synthesis of their precursors (azides and alkynes). Examples of some functional systems based on triazole-containing macrocycles, such as chemosensors, multicalixarenes, amphiphilic calixarenes as well as examples of the use of triazole calixarenes for bioapplications are described.

Keywords

Thiacalix[4]arene, calix[4]arene, azides, alkynes, click-chemistry, CuAAC

1. Introduction

At present, supramolecular chemistry is one of the actively developing branches of modern organic chemistry. Thiacalix[4]arenes and calix[4]arenes are the important macrocyclic representatives of this section. They contain several reaction centers: the upper rim with *tert*-butyl groups and the lower rim with hydroxyls (fig. 1). The abundance of methods for the synthesis of these fragments makes it possible to obtain compounds containing simultaneously different functional groups, while the number of such combinations is undoubtedly huge, which confirms the relevance of the today’s search for new strategies to modify macrocycles. Another important feature of calixarenes is the existence of a number of stereoisomeric forms: *cone*, *partial cone*, *1,2-* and *1,3-alternate*, which opens up the possibility of obtaining both conformationally rigid/flexible systems with different spatial arrangement of functional groups, depending on the introduced substituents (fig.1). For calix[4]arenes, four aromatic rings form a hydrophobic cavity with a volume of one cubic nanometer, while for thiacalix[4]arenes it is 15% larger, which is associated with a bigger sulfur atoms [1,2]. This feature makes it possible to use these compounds as "hosts" for selective binding certain "guests" [3,4]. Such structural features of calix[4]arene derivatives determine the wide application of these macrocycles, and numerous reviews published in the last few years confirm the continuing interest in thiacalix[4]arene and calix[4]arene derivatives. Calixarene derivatives can be used to create chemosensors [5] including fluorescent ones [6,7], macrocyclic ligands for the uses of coordination chemistry [8,9] and efficient catalysts for organic reactions [10,11]. Also, the thiacalix[4]arene and calix[4]arene platform is promising for some branches of biomedicine [12]. It is possible to use these compounds for recognizing biomolecules [13,14], and as a transport for targeted delivery of gene material and drugs [15-17].

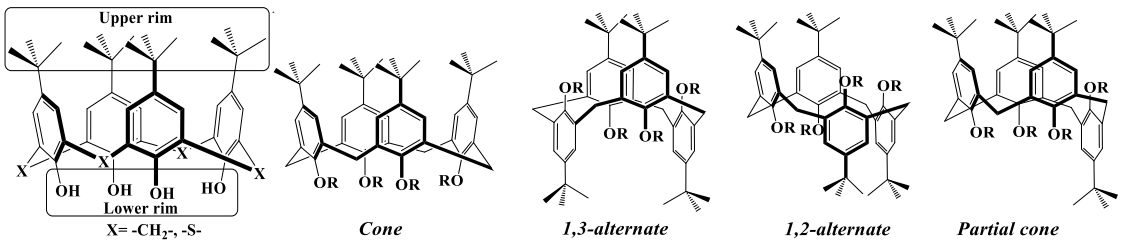


Fig. 1 Structure of thiacalix[4]arenes and calix[4]arenes and possible stereoisomeric forms

Introduction of azide or alkynyl fragments into the structure of calix[4]arenes makes it possible to use these macrocycles as reagents in CuAAC reactions to obtain a wide range of substances [18]. In addition, it opens up the possibility of gently introducing polar groups into the structure of calixarenes and, thereby, obtaining water-soluble compounds, which correspond to the principles of green chemistry and make it possible to carry out complex organic reactions in water [19]. Synthesis of macrocycles capable of selectively recognizing biomolecules is an urgent task for modern scientists. For example, adenine-containing nucleotides play an important role as a universal energy source and intracellular mediator of many biological processes [20]. The synthesis of positively charged calixarenes, due to the introduction of ammonium functional groups into their structure, makes it possible to use these triazole-containing compounds to recognize adenosine diphosphate (ADP) and adenosine triphosphate (ATP) anions with the naked eye [21]. The search for compounds capable of binding another important biopolymer, DNA and RNA, is also an urgent problem. Compounds capable of compacting and reducing its transcription are used in medicinal chemistry for the treatment of cancer and targeted drug delivery [22]. For these purposes, it is possible to use amphiphilic triazolyl macrocycles, which effectively bind DNA molecules, and can reduce its size, while introduced into supramolecular system [23]. All these factors prompted us to write this review, which is devoted to CuAAC reactions on thiacalix[4]arene and calix[4]arene platform.

As mentioned above, Pineda-Castaneda *et al.* recently released a detailed review [18] on the possibilities of modifying polyhydroxylated platforms, such as calix[4]arenes and resorcinarenes, using the CuAAC reaction, focusing mainly on the aspects of synthesis. The main goal of our presented review is to show the versatility of the possibilities of using the “click”-chemistry approach to create functional materials not only on classical calix[4]arenes, but also on the thiacalix[4]arene derivatives. This article reflects the currently possible ways of synthesizing macrocyclic precursors and methods of introducing different numbers of azide, alkyne, and triazole groups into the macrocyclic structure. Also, the possibility of their subsequent application in creation of selective chemosensors, multicalixarenes, amphiphilic systems and compounds with bioapplications is also being considered.

2. CuAAC calixarene precursors

In 2001 Sharpless gave a broad definition of the processes that form the basis of "click chemistry": "click reactions" are model reactions that proceed with good yields under mild conditions, with the formation of stereospecific products [24]. This approach can also be called "imitation of nature" or biomimetics, namely, imitation of the formation of complex biomolecules from a limited number of monomers [25]. Today, modern supramolecular chemistry often uses CuAAC with the formation of 1,4-substituted-1,2,3-triazoles [26]. Such reaction proceeds selectively with good yields, which leads to its wide applications [27,28]. Complex molecules such as thiacalix[4]arenes and calix[4]arenes can also be modified using CuAAC reactions. Using this approach, various functional groups can be introduced into their structure and even bis- or multicalixarenes can be obtained [29,30]. The ease of obtaining triazoles on the macrocyclic platform has led to the widespread use of these macrocycles in the design of hosts for biomolecules [31] and drugs [32], in binding of various metals [33,34] and anions [35]. To obtain triazole-containing macrocycles, an azide or alkynyl functional group must first be introduced into the structure of calixarenes. To date, the literature presents different methods for the synthesis of CuAAC precursors both along the upper and lower rims.

2.1 Alkynylcalixarenes

The main method for introducing a terminal triple bond to the upper rim of macrocycles is the Sonogashira cross-coupling reaction - the interaction of terminal alkynes with aryl halides, where copper (I) and palladium (0) are used as catalysts [36].

To obtain target products, aryl halide derivatives of calix[4]arenes are reacted with trimethylsilylacetylene, while the reactivity increases in series Br<Cl<I. Next step – trimethylsilyl deprotection. For example, the scientific group of Armaroli proposed a synthetic method based on Sonogashira reaction with the use of the iodine derivative **1** (fig 2.) in the presence of triethylamine. The reaction proceeds for 72 h at room temperature with a product yield of 89% [37].

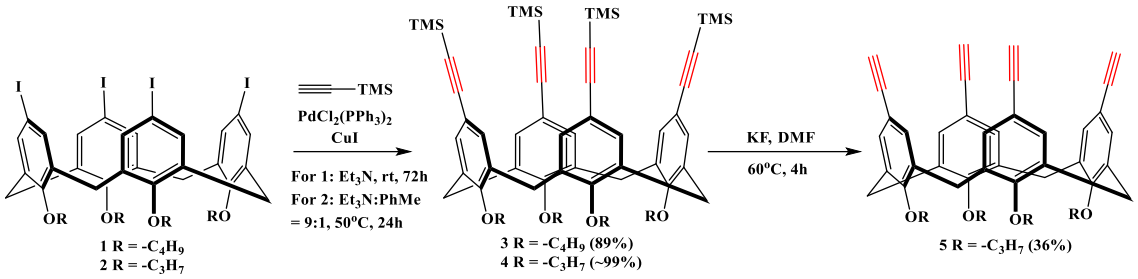


Fig. 2. Synthetic route for introduction of alkynyl groups onto the upper rim of calix[4]arenes

The scientific group of Dondoni carried out the reaction with macrocycle **2** (fig 2.) with heating at 50°C and the addition of toluene as a solvent, which made it possible to reduce the time of complete conversion to 24 h and increase the yield of calix[4]arene **4** to a quantitative [38]. Similarly, cross-coupling is carried out for thiacalix[4]arenes [39] and for the introduction of two alkynyl moieties [40,41].

Silicon has a greater affinity for fluorine than for carbon. Therefore, to remove the trimethylsilyl protective group, compounds capable of generating F- anions, such as KF [38,40] (fig.2) or *n*-Bu_4F [39], are used. Target products are easily isolated from the reaction mixtures by recrystallization from methanol.

An interesting method for the preparation of an tetrasubstituted alkynyl derivative without the use of protective groups was proposed by Kasakova (fig 3.): *O*-propyl calixarene **6** was subjected to Duff-formylation using hexamethylenetetramine (HMTA) in trifluoroacetic acid, then the resulting compound **7** was introduced into the Corey-Fuchs reaction with triphenylphosphine, CCl_4 and zinc. At the final stage bromoalkene **8** was dehalogenated using butyllithium in tetrahydrofuran (THF) to give 53% of the target product **9** [42].

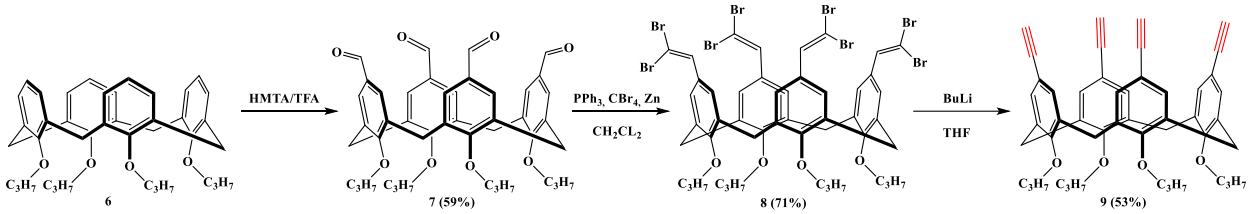


Fig. 3. Production of calixarene-alkynes using the dehalogenation

The introduction of a terminal triple bond on the lower rim of the macrocycles is much easier compared to the upper side due to the possibility of carrying out the classical Williamson`s *O*-alkylation reaction. The most popular reagent for this purpose is propargyl bromide due to its greater commercial availability as opposed to longer chain analogues. To introduce one terminal triple bond (compound **11**, fig. 4), the reaction is carried out in THF in the presence of a mixture of barium oxide and carbonate, to obtain dipropargyl macrocycle **12** (fig. 4) potassium carbonate use as base in acetone or acetonitrile as solvent [43-45]. When all four hydroxyl protons are replaced, the template effect begins to work, which makes it possible to fix the thiacalix[4]arene and calix[4]arene molecules in the required conformation [46,47]. Thus, during the subsequent alkylation of macrocycle **12** (fig. 4) using Cs_2CO_3 as a base, the target product **13** is fixed in the *1,3-alteranate* stereoisomeric form [42], while using K_2CO_3 or NaH, the *cone* **14** is formed [43, 48].

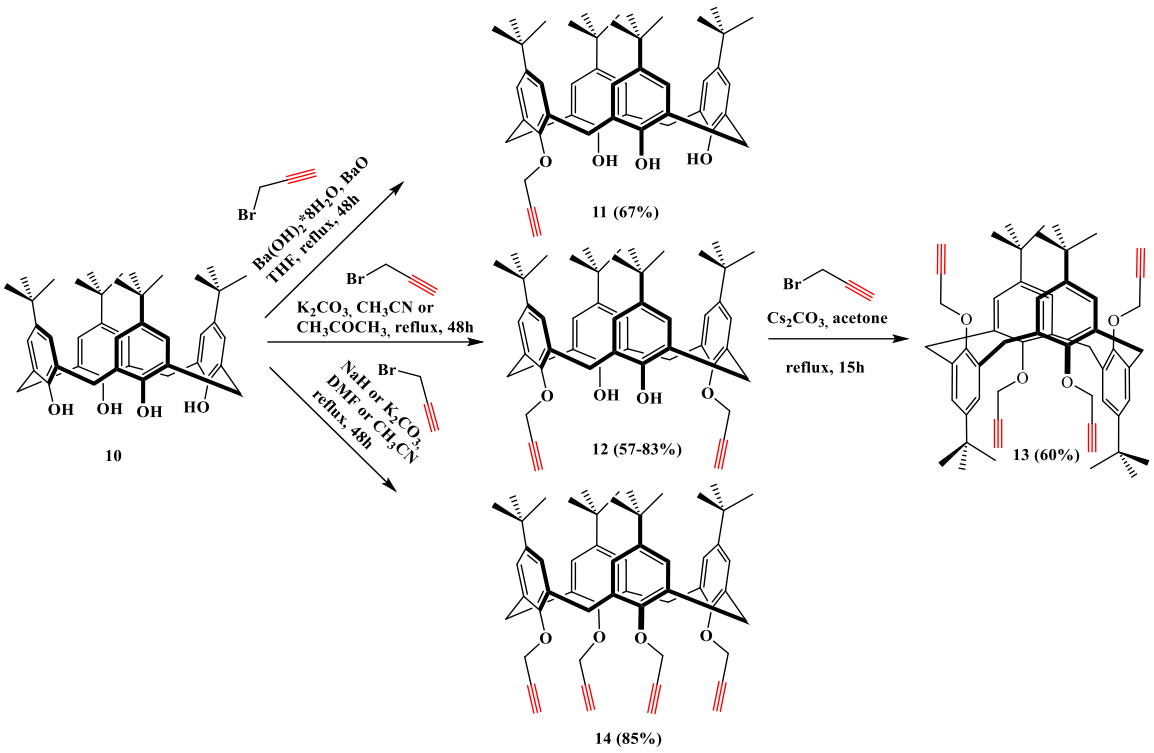


Fig.4. Propargylation on the lower rim of calix[4]arenes

2.2 Azidocalixarenes

The introduction of nitrogen-containing functional groups directly onto the upper rim of thiacalixarene is difficult due to the sensitivity and reactivity of the sulfur atom [49]. Therefore, arylazide derivatives of thiacalixarenes are not presented in the literature. The modification of the classical calixarene is much easier and converts with good yields. In 2003, Zedmard *et al.* proposed a method for the synthesis of a tetraazidomethyl derivative of calix[4]arene using a nucleophilic substitution reaction. The target product is formed in 86% yield [50]. Our scientific group has recently optimized the synthesis of diazidomethyl and azidoimidazolium derivatives of calixarenes with *n*-butyl and *n*-octyl fragments on the lower rim **17** [51,52], and Fujii *et al.* obtained similar tetrasubstituted macrocycle **18** (fig. 6) [53]. But macrocycles with bromine atoms directly on the upper rim, involved in the aromatic nucleophilic substitution reaction with NaN_3, form a mixture of arylazide products [54]. Therefore, the diazotization reaction is the main method for obtaining arylazide derivatives of calixarenes. In Maurin's scientific group, the original amine was dissolved in dilute hydrochloric acid and, when cooled to zero degrees, sodium nitrite was added dropwise. After the addition of sodium azide, the target product was isolated in 91% yield [55]. To obtain the tetrasubstituted product, Buttres *et al.* carried out the reaction under similar conditions with a twofold increase in the amounts of reagents [56]. In this article, the authors for the first time synthesized the so-called "Janus" calix[4]arene **16**, a macrocycle containing simultaneously four propargyl and four azide groups (fig. 5).

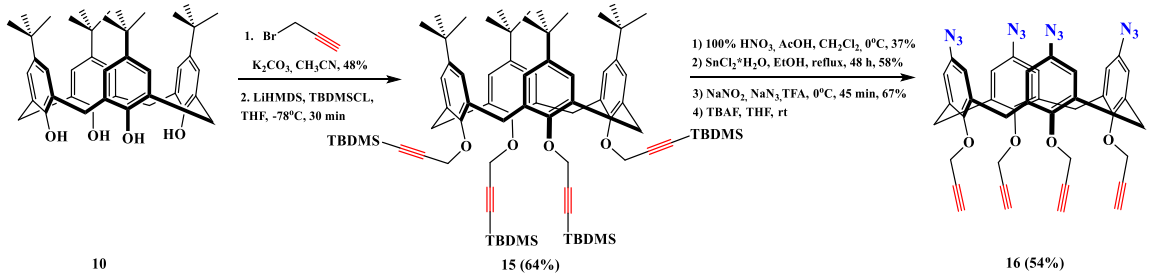


Fig. 5. Synthesis of "Janus" calix[4]arene **16**

Also, our group proposed a strategy for the selective synthesis (fig. 6) of both di- (**17** and **18**) and tetra-azide (**19** and **20**) derivatives of calix[4]arenes; stepwise modification of the calixarene platform through alkylation, nitration, reduction, and diazotization reactions made it possible to obtain target compounds in high yields [21].

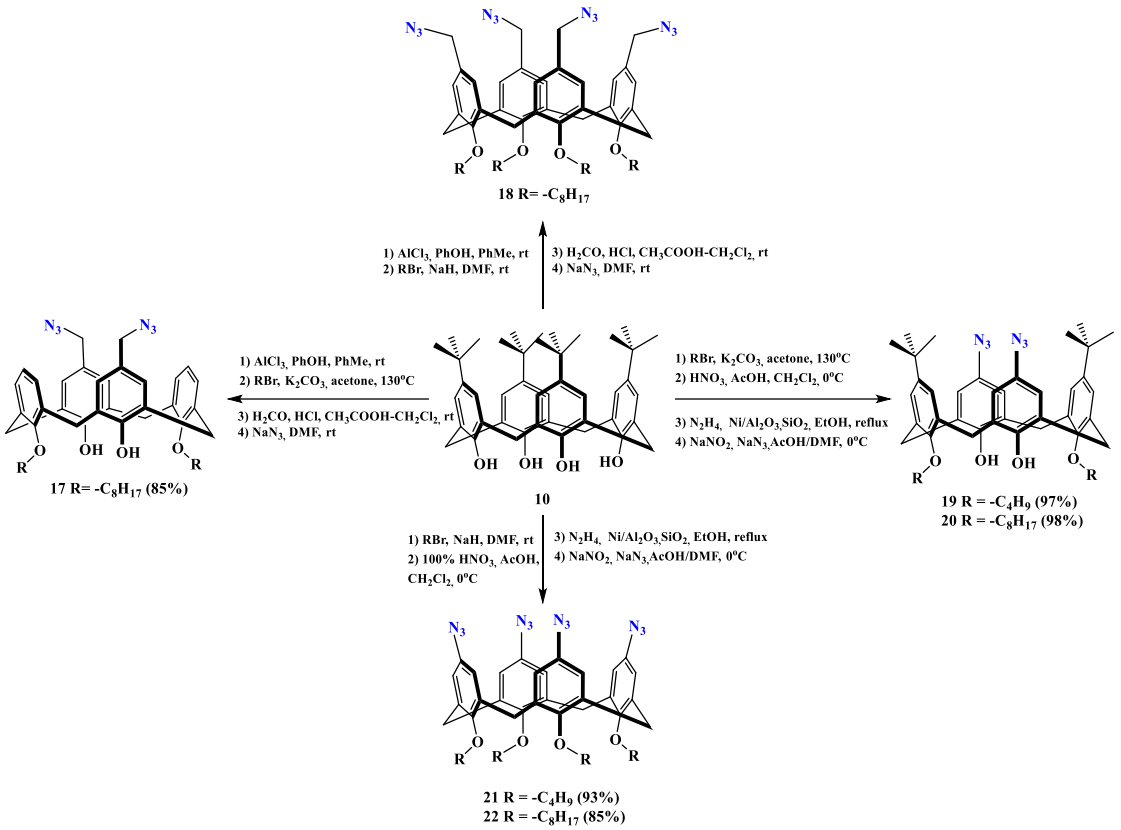


Fig. 6. Methods for synthesis of upper rim azide derivatives of calix[4]arenes

Recently, we have proposed a strategy for the synthesis of tetraazide derivative of calix[4]arene with free hydroxyl groups. Using the approach proposed by Guo`s scientific group [57], amine **24** was synthesized and then introduced into the diazotization reaction (fig. 7). After extraction with chloroform target product **25** was obtained in 80% yield [58].

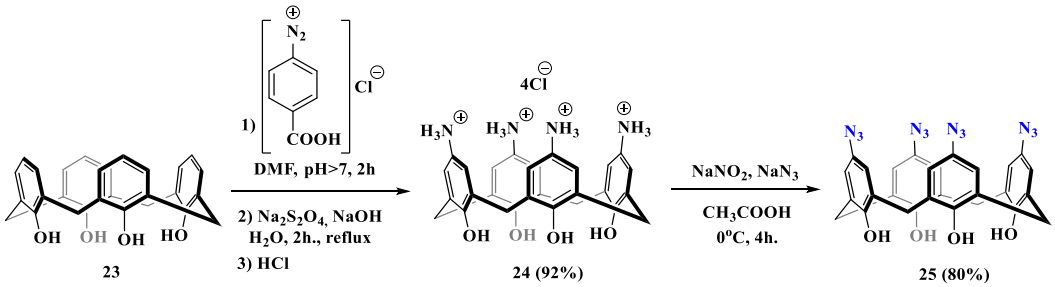


Fig. 7. Synthesis of arylazide calix[4]arene with free hydroxyl groups

It is also possible to obtain monosubstituted arylazide derivatives of calix[4]arenes. For this purpose, Jurich *et al*. proposed a method for the preliminary synthesis of the nitroderivative **26** (fig. 8) using an equimolar amount of nitric acid and a twofold excess of sulfuric acid in dichloromethane in reaction with macrocycle **6** [59]. Stirring at zero degrees for 20 minutes followed by stirring at room temperature for 80 minutes gives compound **26** in 40% yield. As a result of further reduction and diazotization reactions, the target monoazide **28** is formed in quantitative yield. This method opens up the further possibility of obtaining monoaryltriazolated macrocycles.

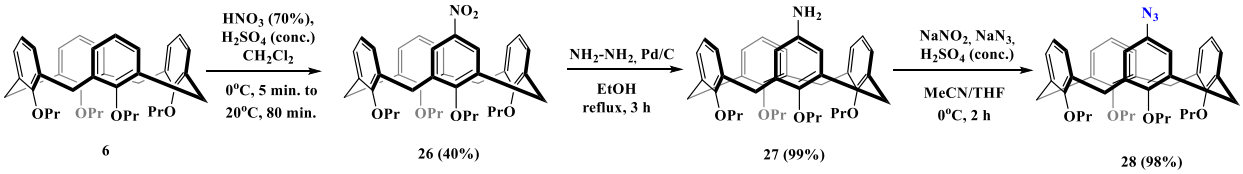


Fig. 8. Synthetic route for obtaining calixarene derivative with one azide group

To date, the most preferred alkyl linker for azide moieties on the lower rim of macrocycles is the ethyl group. To introduce two substituents, the starting calix[4]arene is subjected to an alkylation reaction with

dibromoethane, and then a nucleophilic substitution reaction is carried out using sodium azide [60]. To replace all 4 positions of the lower rim, a more reactive ethyl tosylate fragment is used in the first stage [61]. Ryu and Zhao proposed a synthesis strategy using two successive nucleophilic substitution reactions (fig. 9): *tert*-butylcalix[4]arene **10** is alkylated with ethyl bromoacetate, the resulting ester **29** is reduced with lithium aluminium hydride with formation of alcohol **30**, and the OH-groups are converted into mesylate (compound **31**) and then by the target azide moiety (compound **32**) [62].

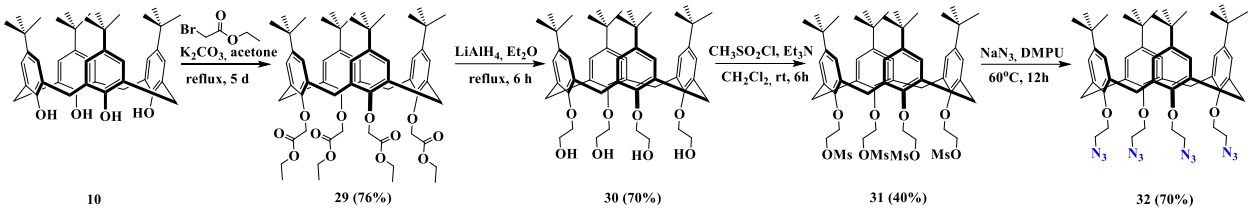


Fig. 9. Synthetic route for obtaining azide containing macrocycles through nucleophilic substitution

A major contribution on the introduction of alkyl azide groups into the lower rim of the macrocycle was made by the scientific group of Vatsuro. They demonstrated the possibility of selective introduction of one, two, three, and four azide fragments [63]. In addition, a number of propyl- and butylazide macrocycles were synthesized according the following procedure (fig. 10): preliminary introduction of the propylene fragment, its subsequent oxidation and substitution allows to obtain propylazide calixarene **35**, and the preparation of bromobutyl derivative **37** with foregoing treatment with sodium azide in dimethylformamide (DMF) allows to synthesize tetrabutylazide containing macrocycle **38**. Calix[4]arenes containing two propargyl groups and two ethyl, propyl, or butylazide fragments on the lower rim were also obtained [64]. The authors demonstrated the possibility of propargylation of lower rim after the initial modification on the upper rim of macrocycles [65].

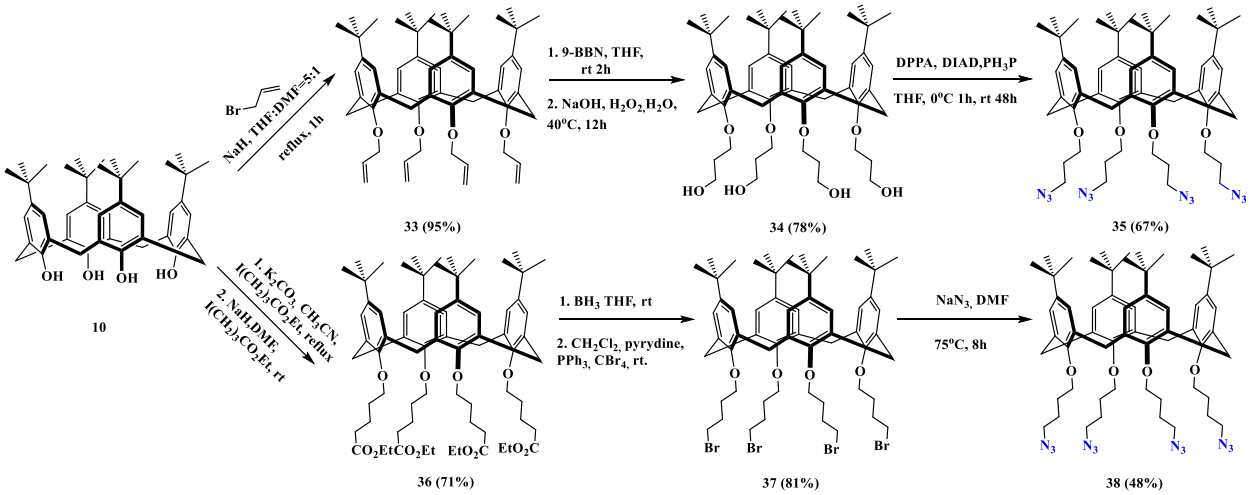


Fig. 10. Synthesis of lower rim substituted tetraazide macrocycles

In 2015 [66], a strategy for the preparation of thiacalixarenes containing two alkyl and two propylazide fragments in the *1,3-alternate* stereoisomeric form was formulated by our research group. To do this, *p-tert*-butylthiacalix[4]arene **39** (fig. 11) was first stepwise reacted with terminal alkyl alcohols and then with 3-bromopropanol-1 under Mitsunobu reaction conditions. Next, a nucleophilic substitution was carried out with sodium azide under microwave heating to give target macrocycles **40-42** in good yields.. In 2016 [67], we figured out that the usage of 3-azidopropanol-1 under the same Mitsunobu conditions results in disubstituted macrocycle **44** in *cone* stereoisomeric form. Recently [68] it has been proposed to use a similar synthetic strategy to prepare tetra-propylazide containing thiacalix[4]arene **43**

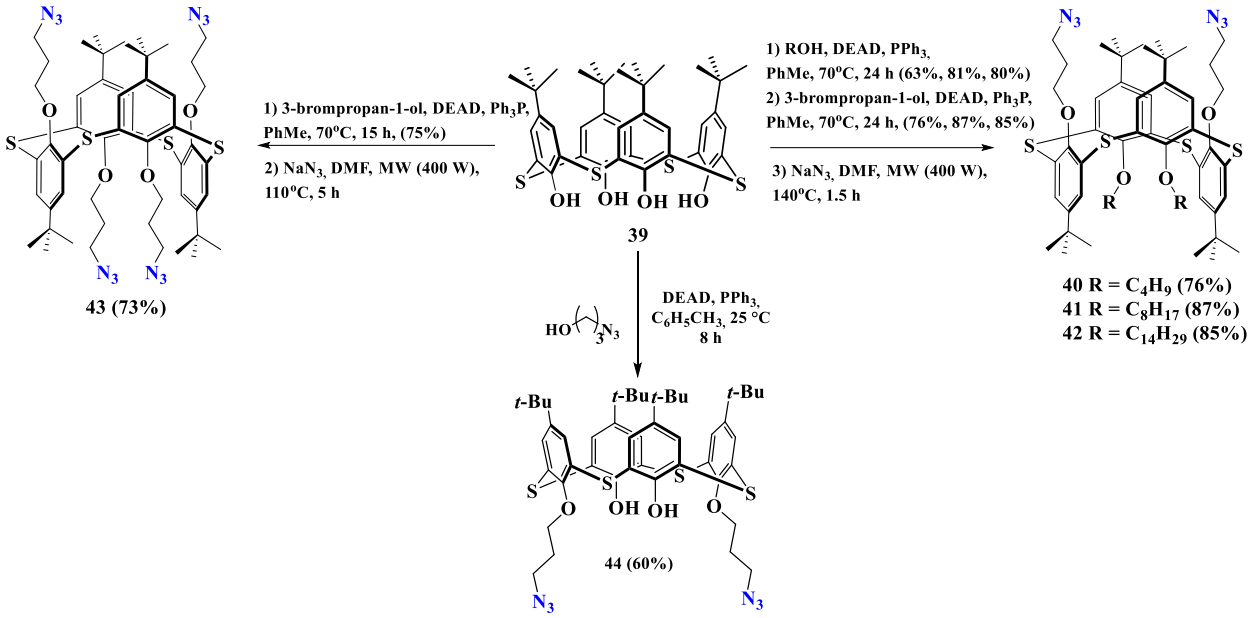


Fig. 11. Synthesis of lower rim substituted azidederivatives of thiacalixarene

It is also possible to introduce azide moiety onto the bridge units and *meta*-positions of macrocyclic platform (fig. 12). So, Hardman *et al*. [69] and later Fischer and Weber [70] proposed to use common lithiation and substitution technique [71] with 1-bromo- ω-chloroalkanes as electrophiles and tetramethylated macrocycle **45** as starting material. Using this approach, the excess of electrophile does not induce dimerization and chlorinated calix[4]arenes **46-48** form in 68 to 85% yields. After the substitution with NaN_3 in DMF and further recrystallization from methanol, target azides **49-51** formed as white powders. Addition of azide moiety to the *meta*-position of substituted aryl fragments succeeded by Lhotak`s scientific group [72]. For this, monoamine **27** was introduced into substitution with trimethylsilyl azide (TMS-N_3) and *tert*-butylhydroperoxide (TBHP) using CuBr as a catalyst at room temperature in toluene. Stirring for 15 min give mixture of products with predominance of **52**. After adding the quadruple excess of both reagents and the increase of the reaction time to 20 min the only product was **53** in 87% yield.

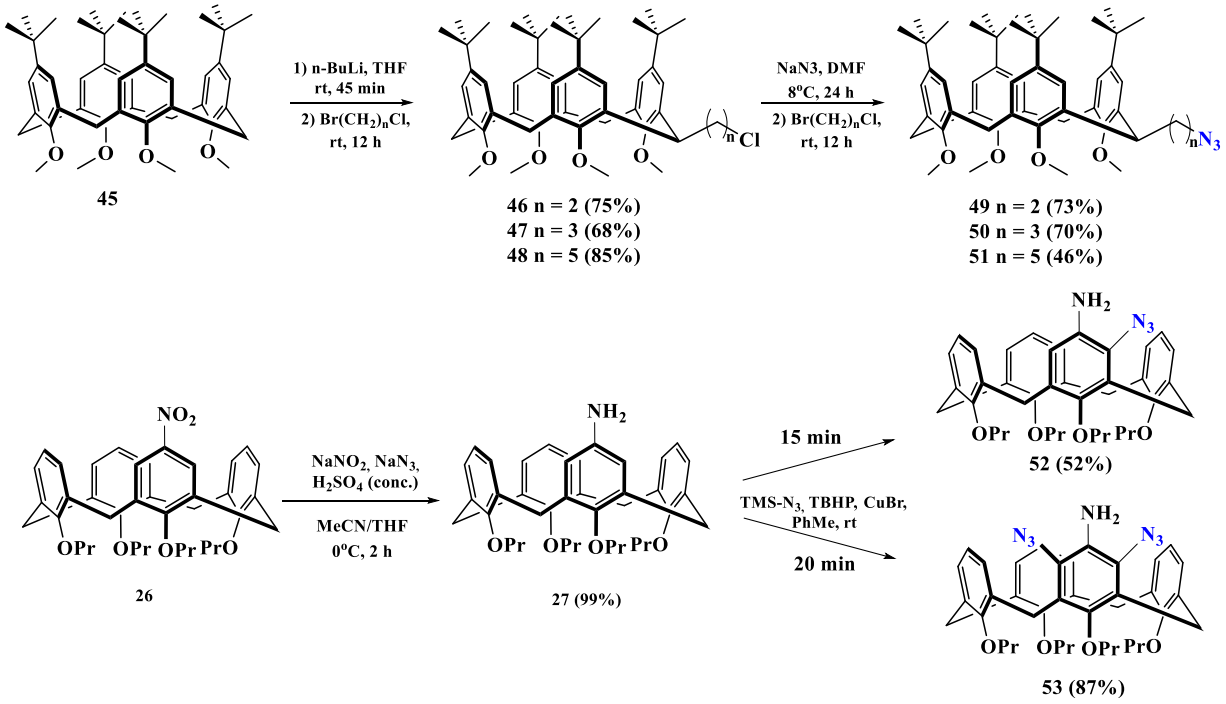


Fig. 12. Modification of calix[4]arene bridge units and *meta*-position with azide moiety

3. Synthesis and applications of triazoles

In the literature, to obtain triazole derivatives of calixarenes, the azide-alkyne cycloaddition (AAC) reaction is mainly used with copper (I) compounds (CuAAC) rather than ruthenium (II) ones (RuAAC) (fig. 13) as a catalysts, which is associated with greater commercial availability of the copper-containing reagents. The reaction takes place over a wide temperature range and usually does not reach 90°C, however, in some cases, the authors successfully used the microwave heating [73,74]. It is possible to use both compounds where copper exhibits an +1 oxidation state, as well as *in situ* generation of copper (I) ions. For the first case, CuI is the main reagent [67,75], however, more complex catalysis systems are also used. To generate ions *in situ*, a system consisting of a divalent copper salt ($CuSO_4$, $CuBr_2$) and a biologically harmless reducing agent (for example, sodium ascorbate (AscNa)) is usually used [76,77]. In some cases, when using activated alkynes with electron acceptor groups, the reaction does not require the use of catalysts [19, 78].

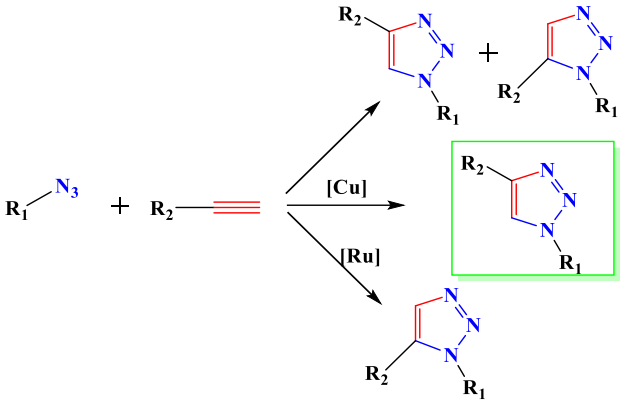


Fig. 13. Schematic representation of azide-alkyne cycloaddition

3.1 Calixtriazole chemosensors

As mentioned above, the click chemistry approach allows scientists to introduce various functional fragments into calixarene molecules, thereby opening up the possibility of selectively adjusting the size of the macrocyclic structure, so that the resulting system is able to bind and detect target substrates [5]. The literature provides examples of obtaining sensors based on calixarene platforms capable of giving a selective response to specific cations [79,80] and simultaneously detecting a number of metals at low concentrations [81]. In addition, some of such systems are of practical importance, exhibiting anticancer activity and can be used for biomedical purposes [82]. So, in this section chemosensors based on calixarene triazoles are discussed.

In 2014, Maurin`s research group presented the CuAAC reaction of a diazide calix[4]arene derivative **54** with (N,N,N-trimethylammonium)propargyl hexafluorophosphate, with the use of tetrakis(acetonitrile)copper(I) hexafluorophosphate - 2,6-dimethylpyridine catalytic system (fig. 14). Using ^{1}H NMR spectroscopy authors defined that the synthesized macrocycle **55** can interact with Cu^+ ions. **55** was found highly soluble in water and demonstrated efficient binding of copper(I) ions from aqueous solutions at pH = 7.4. At the same time, the binding process proceeded selectively with respect to other metals with the stoichiometry ligand:copper = 1:1, and complex **56** was found insensitive to an air [55].

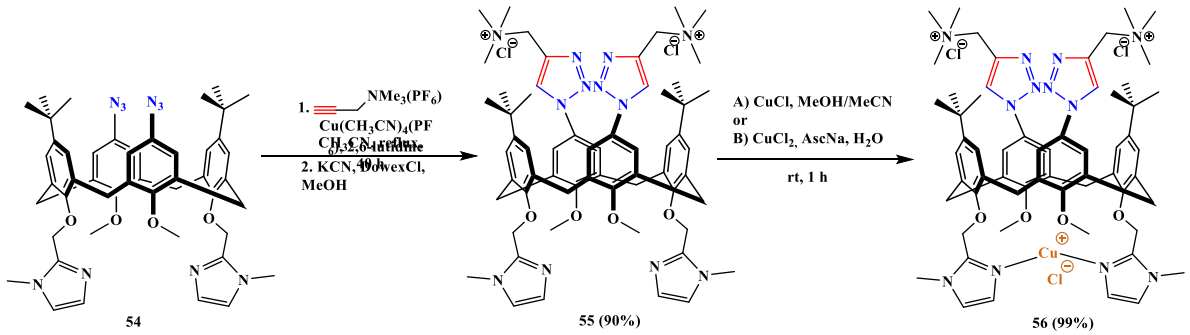


Fig. 14. Synthesis of ligand for Cu (I) binding

Another copper-selective sensor based on the classical calix[4]arene platform was synthesized by the authors of [83]. To obtain the target macrocycle **59** (fig. 15), dipropyl azide **57** was reacted with propargyl containing coumarin **58** in acetonitrile:water=2:1 at 90ºC for 6 h. Catalytic Cu^+ ions were generated *in situ* using the

system $CuSO_4$/AscNa. The obtained triazole-containing macrocycle showed effective interaction with copper (II) ions in comparison with a number of other metals. The complex stoichiometry **59**:Cu was found as 1:1 with the detection limit around 10^{-7} M. Also, the authors demonstrated the possibility of using macrocycle **59** as a sensor for the detection of copper ions in human blood serum with the 90-100% recovery.

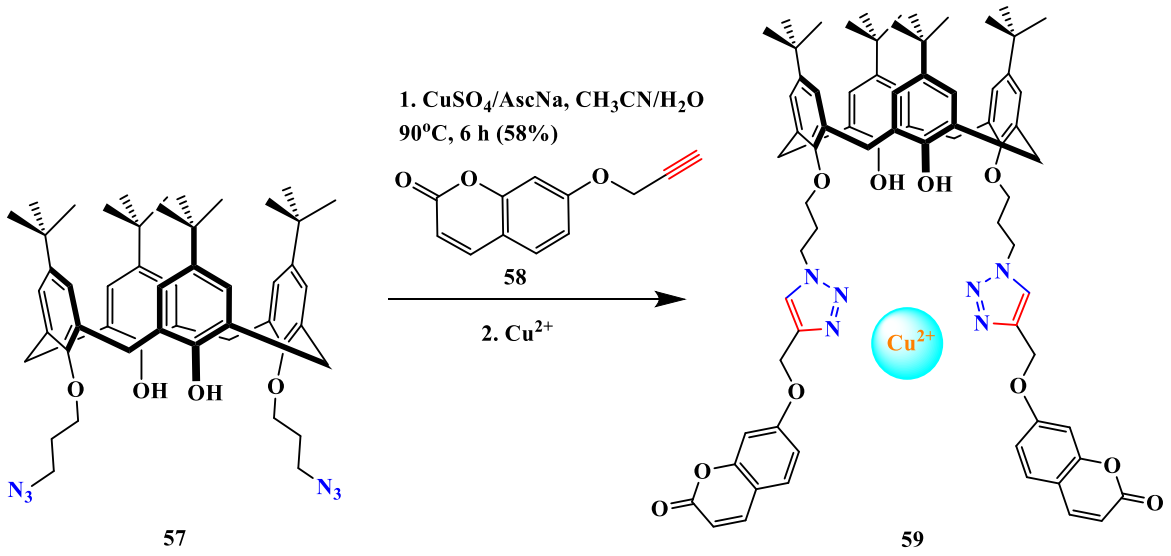


Fig. 15. Synthesis of macrocyclic sensor **40** for Cu (II) detection in human blood serum

Thiacalix[4]arene derivatives can also be used as chemosensors for copper ions. For these purposes, Zhao *et al.* [84] proposed to use the macrocycle **61** (fig. 16) in the *1,3-alternate* stereoisomeric form containing two pyrenyltriazole fragments and two carbonyl groups for additional binding. Target product was formed under the CuAAC-reaction conditions between thaicalixarene **60** and 1-(azidomethyl)pyrene (fig. 16). The resulting compound **60** in ethanol showed the possibility of selective determination of Cu^{2+} in a ratio of 1:1 with a detection limit comparable to that of the analogue on the classical calix[4]arene platform. Using ^1H NMR spectroscopy, the authors determined that in the presence of ethylenediamine, the free form of ligand is released, indicating thus reversible complexation.

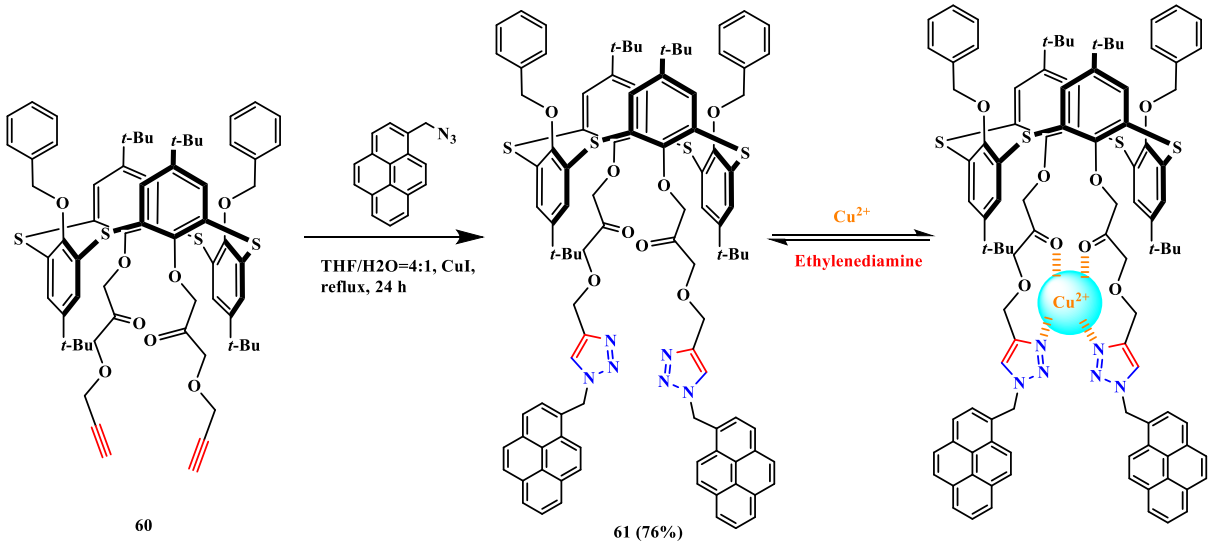


Fig. 16. Reversible Cu^{2+} chemosensor based on thiacalix[4]arene platform

Another example of the selective binding of metals is presented in the work of Alodhayb`s scientific group [85]. To obtain macrocycle **63** containing anthracene fragments, calix[4]arene **62** was introduced into the CuAAC reaction in the THF/H_2O system with copper (I) iodide as a catalyst at 60°C for 24 h. The resulting compound **63** was found to form self-assembled monolayers on a gold surface. The resulting system showed high sensitivity to Hg^{2+} ions in aqueous solutions. The minimum detection limit was 10^{-13} M. According to density functional theory (DFT) calculations, the mercury atom is located between four binding sites - two -OH and two triazole fragments (fig. 17).

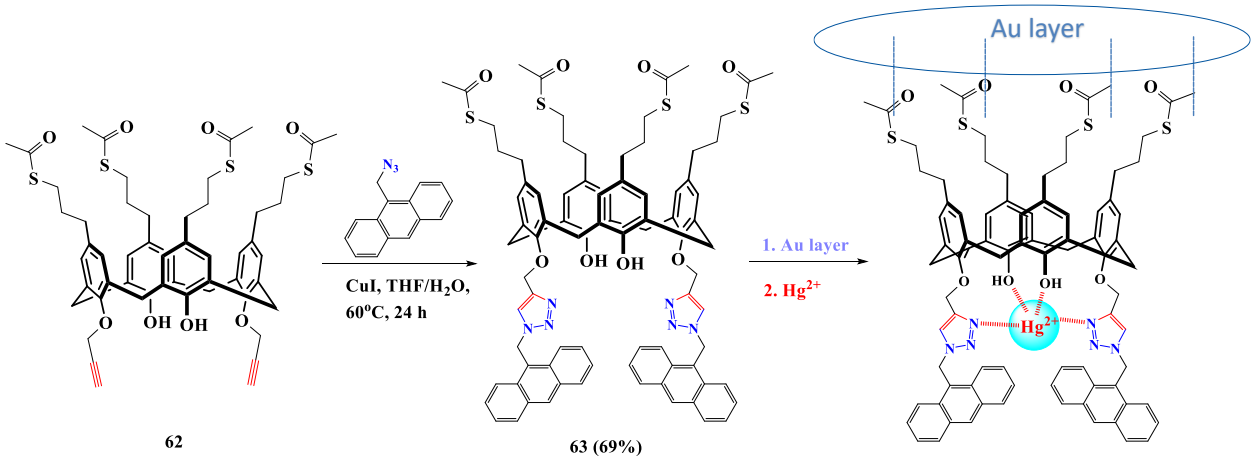


Fig. 17. Synthesis of macrocycle, sensitive to Hg^{2+} cations

In 2020 [86], Chen's scientific group synthesized bidentate ligands based on classical calixarene, capable of binding not only mercury, but also silver ions. The structure of macrocycles **64**,**65** contains two binding 1-(pyren-1-ylmethyl)-1H-pyrazole and benzyltriazole fragments, which can bind two substrates simultaneously, as shown in figure 18. The fluorescence experiment showed that interaction with a mercury causes strong quenching of fluorescence whereas silver results in two times less quenching compared to the mercury. Therefore, the resulting macrocycle is a promising fluorescent sensor for homoditropic determination of Hg^{2+} and Ag^{+} ions. Selective sensors for only silver ions on a thiacalix[4]arene platform were obtained by the authors of [87]. In chloroform, a preliminarily self-organizing system (fig. 18) is able to bind one cation on the upper and one on the lower rim due to the presence of two binding centers. The resulting complex **66** forms stick-shaped aggregates, which are potentially applicable to design sophisticated polymeric materials with excellent responsive properties for Ag^{+}.

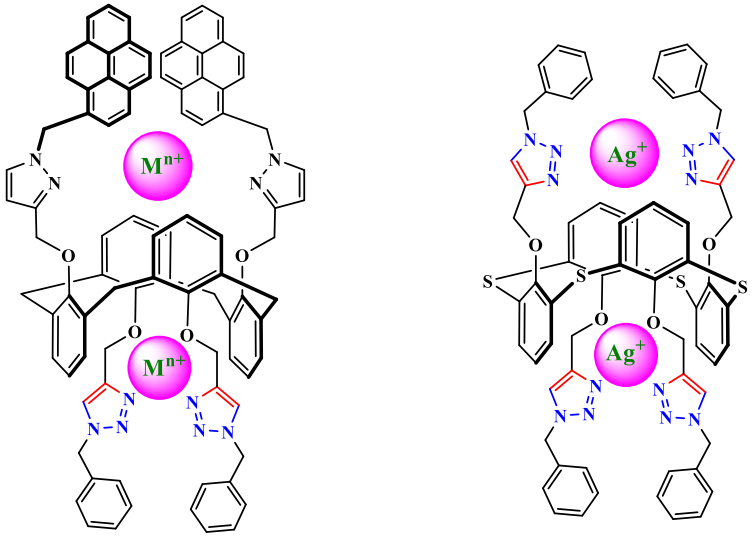


Fig. 18. Calix[4]arene and thiacalix[4]arene complexes with Ag^{+} and Hg^{2+}

Hexanuclear silver (I) complex on thiacalix[4]arene platform with M:L ratio of 6:2 was obtained by Ovsyannikov *et al.* [88]. To synthesize target ligand **68** (fig. 19) tetrapropargyl macrocycle **67** was introduced into reaction with *para*-nitrophenylazide. The reaction was carried out under 80°C for 17 h. An interesting fact is that during this transformation, the initial macrocycle undergoes conformational changes passing from the stereoisomeric form 1,*3 alternate* to a *cone*. The authors suggest that this may be due, firstly, to the large size of thiacalix[4]arene compared to the classical one, which contributes to an easier change in conformation, and secondly, to the possible template effect of the copper (I) ion.

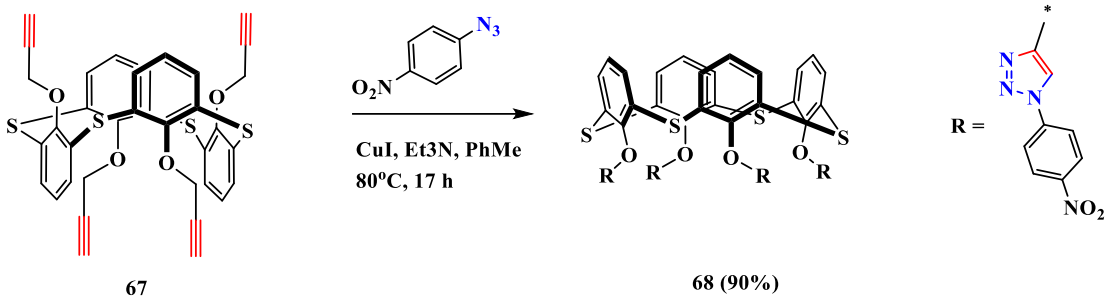


Fig. 19. Change in the conformation of thiacalix[4]arene during the CuAAC reaction

The preparation of monotriazole derivative of calix[4]arene and a further attempt to obtain *meta*-ruthenium compound was undertaken by the authors [59]. To this end, monoazide **29** was reacted with phenylacetylene (fig. 20) followed by quaternization with methyl iodide. The metallization reaction was carried out according to the method of the scientific group of Albrecht [89], but the product **70** was found unstable. However, its existence was determined by high-resolution electrospray ionization mass spectrometry (HRESI-MS), where peaks of the whole molecular cation **70**, as well as cations of complexes directly related to triazole ring without affecting the *meta*-position of the substituted aromatic fragment were recorded.

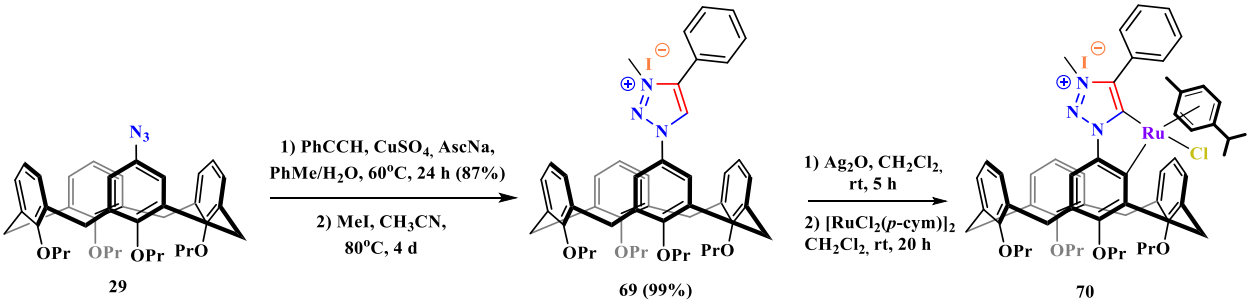


Fig. 20. Meta-metallation of monotriazolium derivative of calix[4]arene

As mentioned above, CuAAC reactions can be used to create substrates capable of recognizing various anions. Cyclic chelate macrocycle **73** was synthesized by Nehra *et al.* [90]. At the first stage, a "click"-reaction was performed between the calixarene **12** and azide **71** (fig. 21) in a two-phase dichloromethane/water system at room temperature; then the intermediate product was reacted with *O*-phenylenediamine in methanol to form cyclic imine **72**, which turned out to be a selective receptor for Mg^{2+} cations. After reduction of the imino groups with sodium borohydride, the target amine **73** was formed in 50% yield. Macrocycle **73** demonstrated binding abilities towards CO_3^{2-}, HCO_3^-, $CH_3CO_2^-$, and F^- anions, while the greatest interaction was observed for the dihydrophosphate anion $H_2PO_4^-$, selective in the presence of other biologically active phosphates anions.

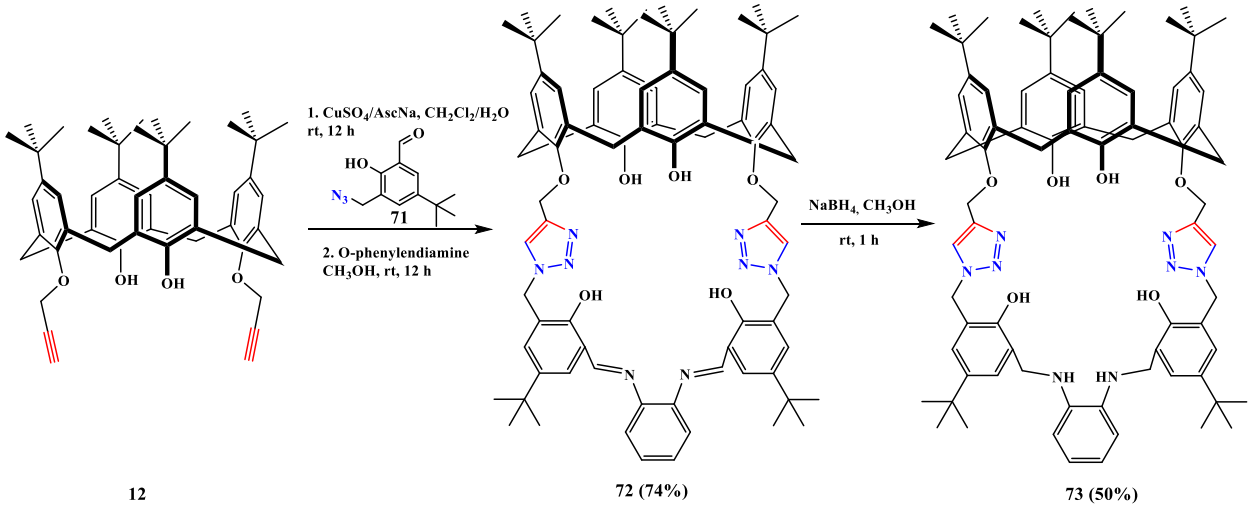


Fig. 21. Synthetic route for macrocycle **73**, responsive to $H_2PO_4^-$

Another example of the macrocyclic chemosensors, selective to anionic species is presented in [91]. The authors introduced fragments of ferrocene into the structure of a tetrasubstituted macrocycle **74** containing four azidoacetamide groups (fig. 22). Copper sulfate/sodium ascorbate was also used as the catalytic system, and a mixture of DMF:water=4:1 served as the reaction medium. After recrystallization, the target product was isolated in 91% yield. The resulting macrocycle **75** showed a high binding selectivity with respect to the fluorine anion with a limit of detection 2.98×10^{-6}. The authors suggest that the fluorine anion in complex **76** binds due to interactions with triazolic C-H and amide N-H bonds.

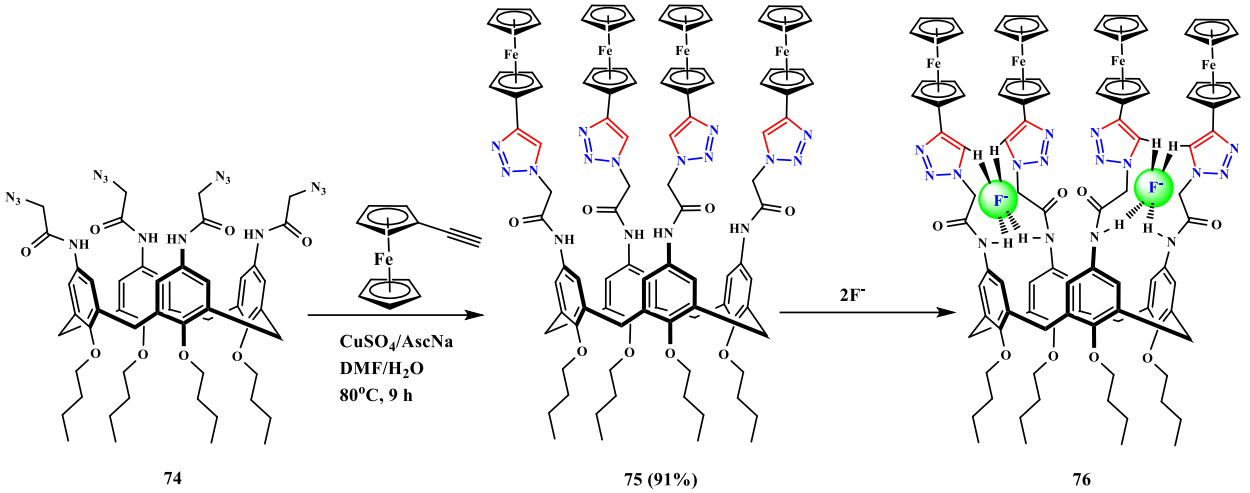


Fig. 22. Calix[4]arene **75** capable of binding F^- and proposed binding mode **76**

As noted above, our scientific group has formulated a procedure for the synthesis of aryl azide derivatives of calix[4]arenes with alkyl groups on the lower rim. In [21], polyamine macrocycles in the *cone* stereoisomeric form **77**,**78** and **81**,**82** were obtained using CuAAC reaction (fig. 23). After removal of the *tert*-Butyloxycarbonyl (Boc)-protecting groups, target products **79**,**80** and **83**,**84** were formed in 86–93% yields. Further, the ability of the obtained ammonium salts to bind biological phosphates was studied. An interesting observation was that disubstituted calix[4]arenes **79** and **80** bind the less charged ADP much better than ATP.

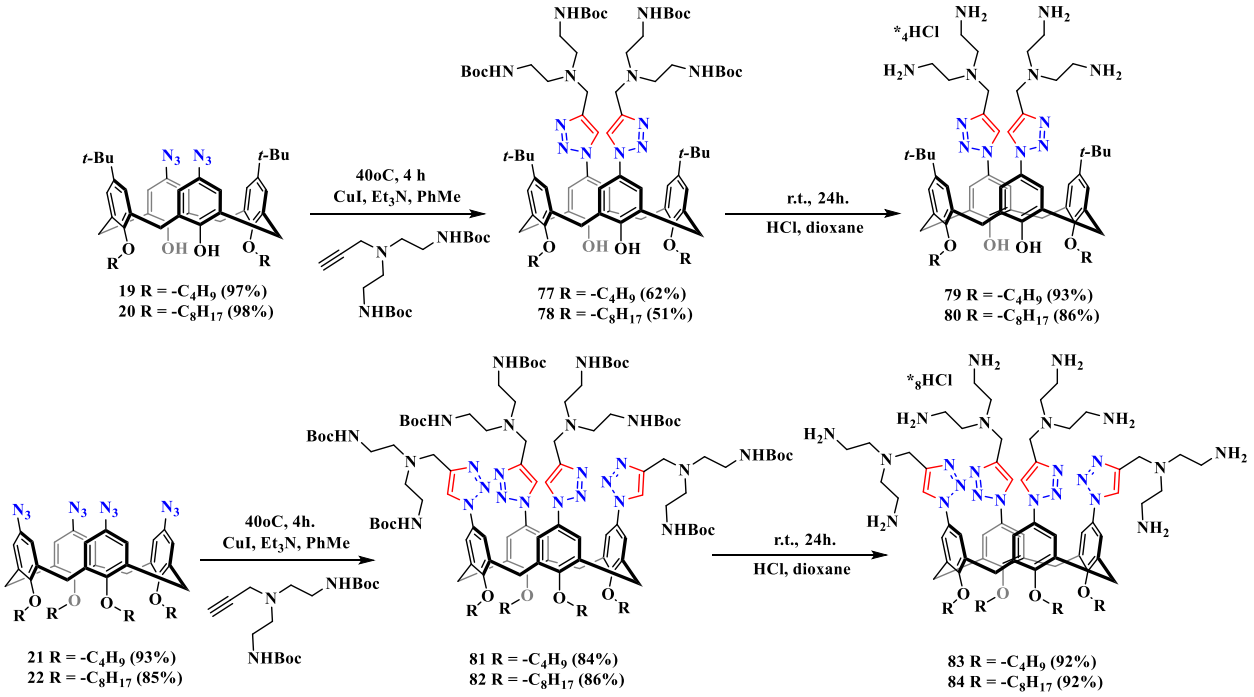


Fig. 23. Synthethic route for obtaining polyamine macrocycles **79**,**80** and **83**,**84** with lipophilic alkyl chains on the lower rim

Noting this fact, we proposed to use macrocycle **80** as a sensor for ADP molecules. To do this, macrocycle molecules were immobilized on a polydiacetylene matrix. With an increase of the ADP concentration a visual color change can be observed. Thus, the resulting sensor can be used to detect biomolecules with the naked eye (fig. 24).

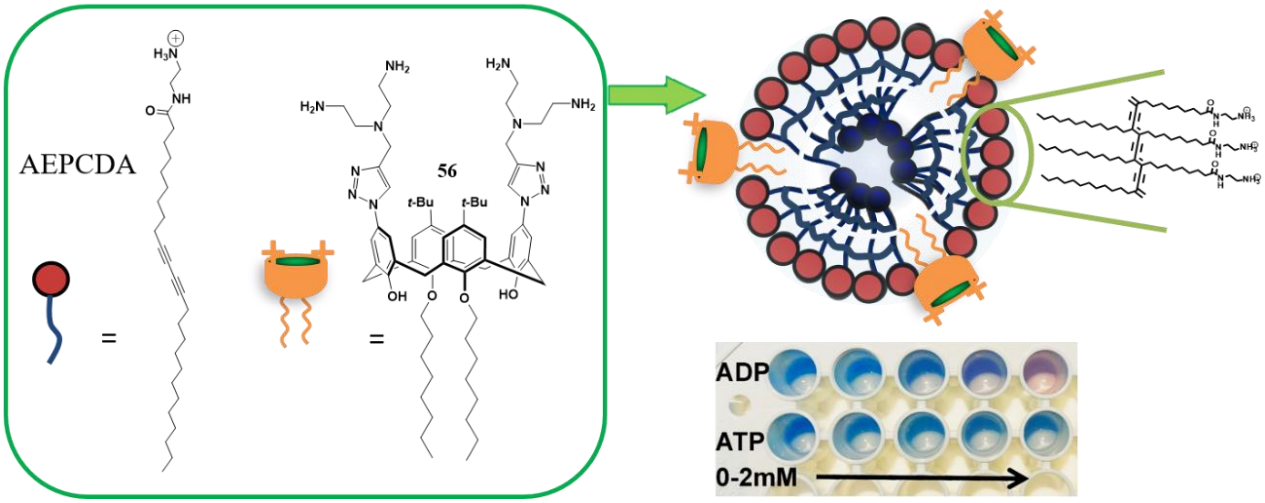


Fig. 24. Naked eye detection of ADP using polyamine derivative of calix[4]arene

Also, introduction of azide or alkyne group into the structure of macrocycles opens up a possibility to perform on-surface click-reactions for creation of functional materials. For example, Feng *et al.* [92] immobilized coumarin containing calix[4]arene **86** on the silica surface (fig. 25). The self-assembled monolayers were created using "click"-chemistry approach – azidomodified surface **85** was immersed into the solution of **86** together with the catalytic system of $CuSO_4$/AscNa in acetonitrile and the resulting mixture was heated at 75ºC for 8 h. The resulting surface **87** showed highly selective macroscopic response towards organophosphate insecticide – phoxim with the detection limit of $1x10^{-6}$ M.

Undoubtedly, the problem of selective recognition, separation and delivery of certain enantiomers of drugs is an urgent problem today. Zhang's scientific group proposed a new method to control the chiral delivery of naproxen enantiomers and convenient recognition of S-naproxen. [93]. Macrocycle **88** with two S-mandelic acid moieties was immobilized on the structured silica surface **85** *via* "click" reaction. The resulting system **89** exhibited an enantioselective ability to recognize S-naproxen in aqueous solutions in the concentration range $4x10^{-6}$ – $1.0x10^{-4}$. Authors suggest that this enantiomer is able to interact with the calixarene molecule due to guest-host interactions, while R-naproxen is not able to linger on the formed surface.

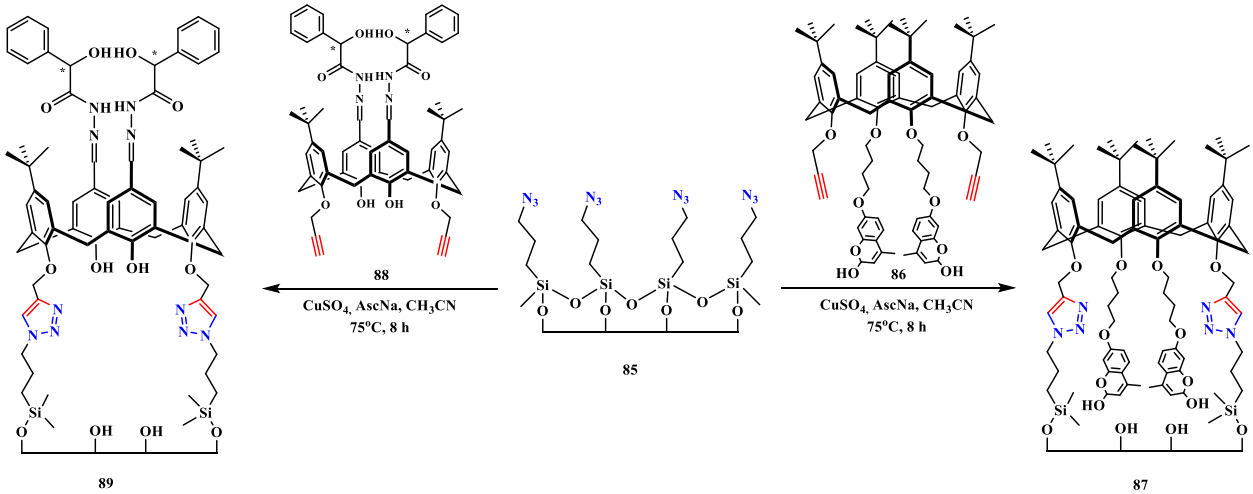


Fig. 25. On-surface click reaction used to obtain functional materials based on calix[4]arenes

Thus, the area of application of the click chemistry approach on thiacalix[4]arene and calix[4]arene platforms for the creation of chemosensors is truly enormous. In addition to the articles discussed above, we consider it important to note the possibility of thiacalixarene and calixarene triazoles to detect lanthanides ions [94], Fe (III) or Al (III) ions depending on the analysis medium [95], on-off switchable fluorescent sensors for K^+/Pb^{2+}

[96], as well as selective calix[4]crowns towards Pb^{2+} and alkali metals [97]. So, calixtriazoles are ideally designed for the use as chemosensors for detection of different compounds, ions *etc*., therefore their relevance in the synthesis of the new water-soluble sensor systems is undeniable. The CuAAC approach can help to construct them, since it allows to arm the macrocycle with any necessary functional fragments to tune selectivity/sensitivity/solubility.

3.2 Multi calixtriazoles

The CuAAC reaction can be used to synthesize multi-calixarenes. Morales-Sanfrutos *et al*. obtained a number of cavitands on the macrocyclic platform **93-95** from the dipropargyl derivative **12**, as shown on figure 20. The authors used a monovalent copper complex [$(EtO)_3P$*CuI] in toluene as a catalyst. The main reaction products are cyclic derivatives **90-92**. In the same work, using the CuAAC reaction, bis-calixarene **96** (fig. 26) as well as ferrocene-containing macrocycles **97**,**98** were obtained in good yields [98]. The scientific group of Camilleri succeeded in synthesizing macrocycle **101**, cross-linked on the upper rim (fig. 20) by carrying out the reaction between monosubstituted alkyne **99** and azide **100**. The $CuSO_4$/(AscNa) system was used as a catalyst in the presence of tris(benzyltriazolyl)amine (TBTA) as stabilizing ligand [30].

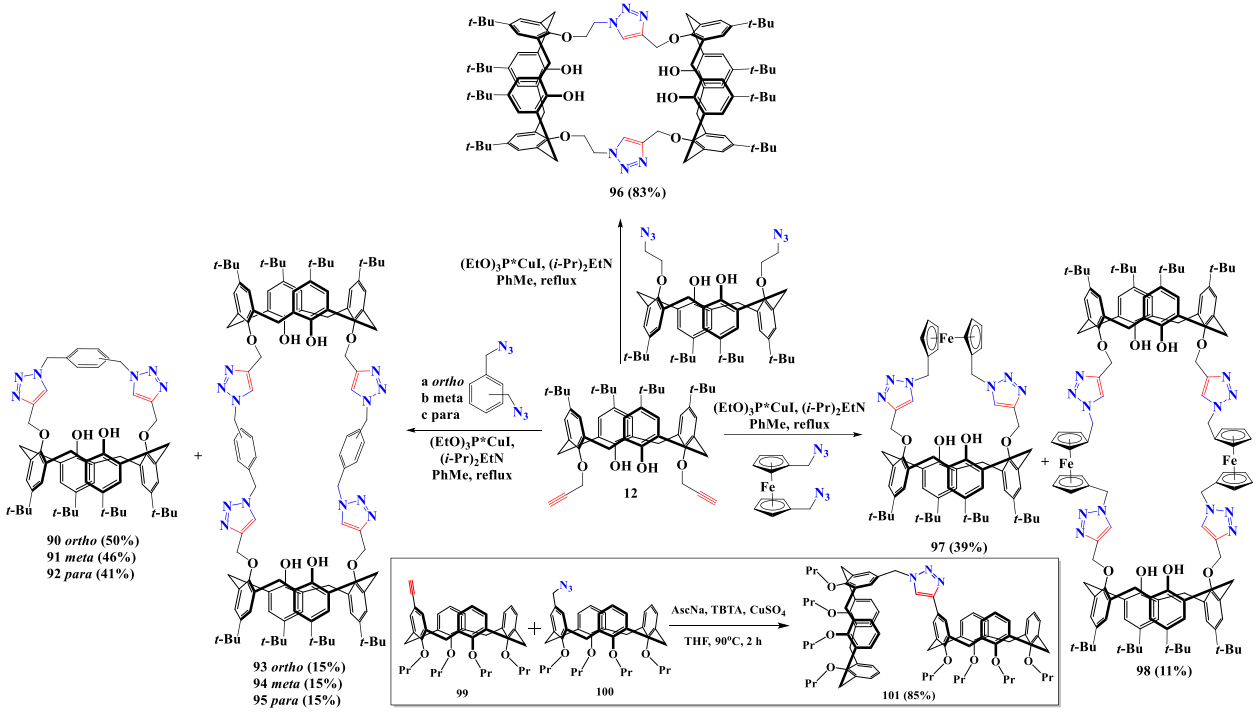


Fig. 26. Synthetic routes for obtaining bis-calixarenes

Another example of lower rim linked bis- and tris-calix[4]arenes are demonstrated in the work of Khan`s scientific group [99]. Authors obtained pincer type ligands on macrocyclic platform, which are now under investigation as potential size-selective and recyclable catalysts for different chemical reactions. To achieve target substances, dipropargyl calix[4]arene **12** was introduced into the CuAAC reaction with 2,6-bis(azidomethyl)pyridine (fig. 27) in DMF/H_2O medium with *in situ* generated Cu^+ through ascorbic acid - copper sulfate (II) - sodium hydrocarbonate catalytic system. After heating at 60°C for 6 h products were purified by silica gel column chromatography with ethyl acetate as eluent. Cyclic macrocycle **103** demonstrate the highest yield (47%), biscalix[4]arene **102** was obtained with 37% yield and triscalix[4]arene **104** took the smallest 10%.

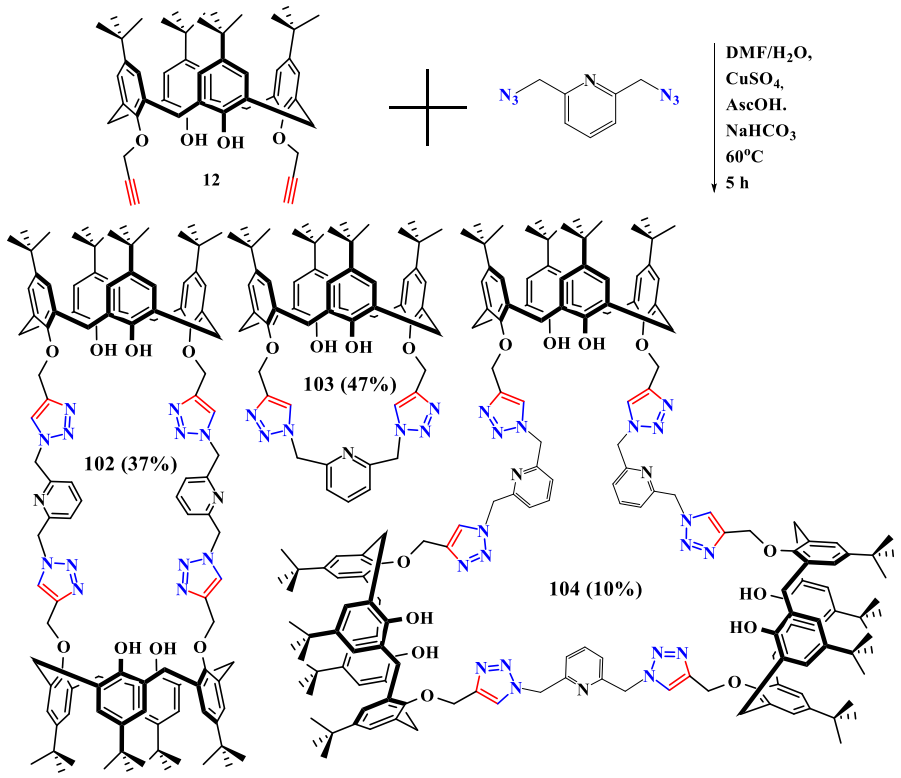


Fig. 27. Synthesis of pincer-type ligands based on mono-, bis- and tris-calix[4]arene

The synthesis of multicalixarenes is also possible on the thiacalix[4]arene platform. Muravev *et al.* [100] synthesized dendrimer-like structures **112-127** and their precursors. As the core, it was proposed to use a macrocycle in the *1,3-alternate* stereoisomeric form containing 4 alkyl or azide fragments (fig. 28 **43,105-107**) with different alkyl linkers. Mono-substituted macrocycles **108-111** or similar macrocycles with an ethyl- or propyl azide moiety were used as a "branches" of the dendrimer (fig. 28). The reactions were carried out under microwave radition at 70°C for 12 h in a toluene/trimethylamine medium; copper iodide was used as a catalyst. Target pentakis-thiacalixarenes **112-127** were formed in yields from 48 to 80%.

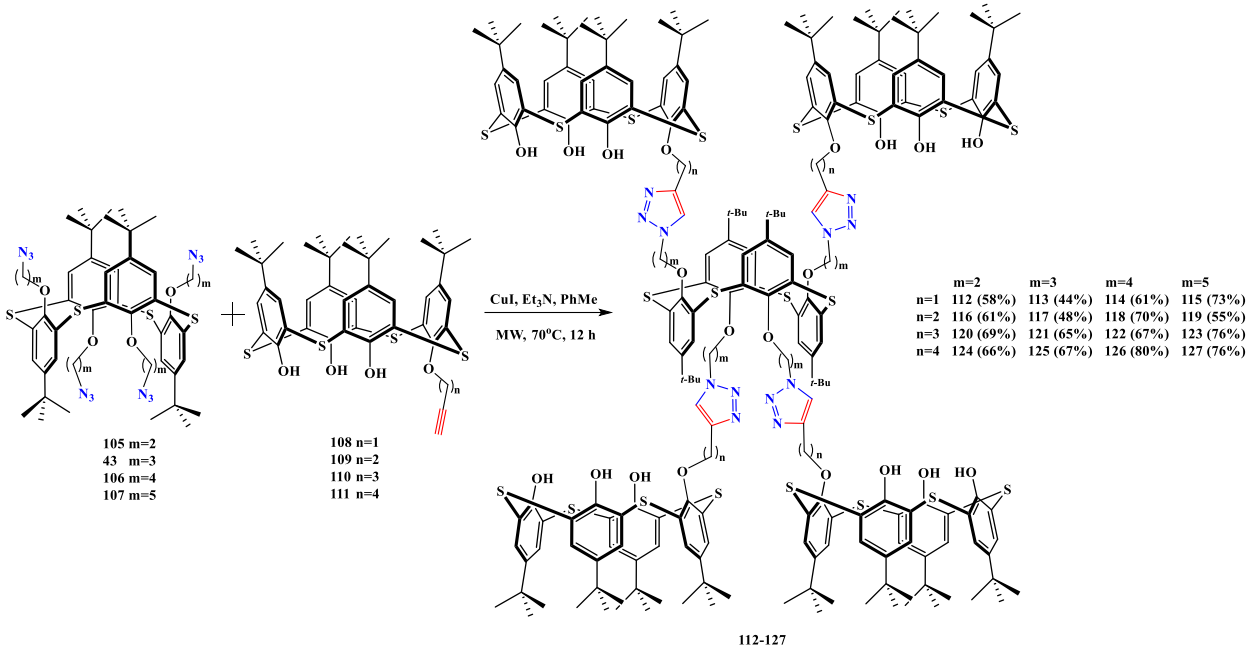


Fig. 28 Synthesis of dendrimer like pentakis-thiacalix[4]arene derivatives

The scientific group of Thulasi synthesized biscalixarene from preliminary obtained macrocycles containing hydroxypropyl azide and hydroxypropargyl groups on the upper rim [101]. Copper (II) sulfate/sodium ascorbate was used as the catalytic system, and freshly distilled *N,N*-diisopropyehylamine was used as the base.

Target macrocycle **130** (fig. 29) was isolated by column chromatography with hexane/ethyl acetate as eluent. Bis-calix[4]arene **132** and tris-calix[4]arene **134** were obtained by reaction with 1,4-diethynylbenzene and 2,4,6-triethynylbenzene, respectively, under similar catalytic conditions. Target macrocycles were obtained in 82 and 76% yields, respectively.

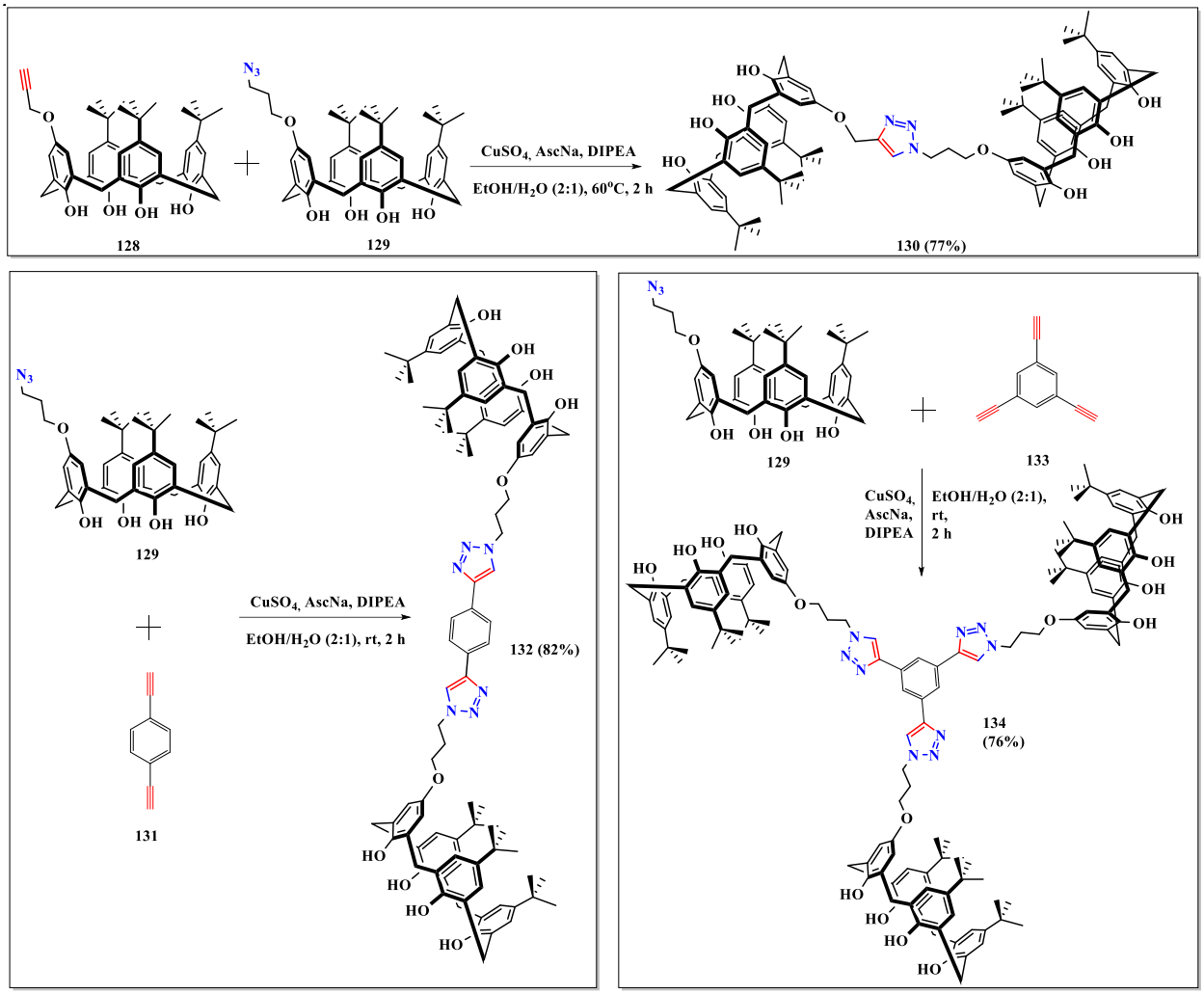


Fig. 29. Bis-calix[4]arenes and tris-calix[4]arene linked by oxyethyl and oxypropyl linkers on the upper rim

As shown above, Fischer and Weber [70] proposed a method for modifying bridging methylene groups with alkyl azide fragments (Fig. 12). They used this approach to prepare bis-calixarene podants with different linker lengths and different intermediate bridging groups using starting alkynes **135**–**137** and azides **49**–**51**. After column chromatography, biscalixarene podants **138**–**142** were isolated in 39–67% yields. Based on NMR spectroscopy data and molecular calculations, the authors concluded that in gas phase compounds **134-138** have a concave cavity which contribute to the potential use as shape-sensitive chemosensors and multivalent devices.

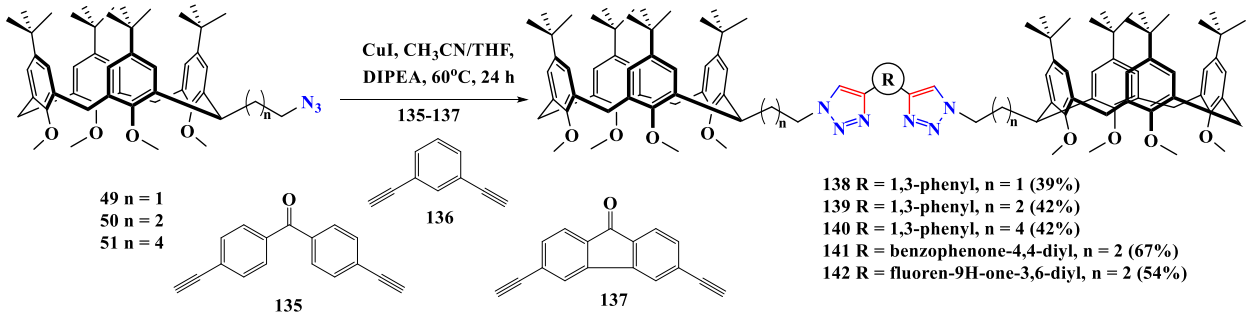


Fig. 30. Synthesis of bis-calix[4]arene podants – potential shape-sensitive chemosensors

"Click"-chemistry makes it possible to obtain structures consisting of several calixarenes and, at the same time, possessing biologically active properties. For example, the authors of [102] synthesized dimer (fig. 31) of

commercially available calixarene 0118, which is currently used to treat cancerous tumors [103]. For this, macrocycle **143**, containing a propargyl fragment attached directly to the methylene bridge of calixarene, was obtained. Then, two calixarenes **143** were crosslinked with diethyl azide–diethylene glycol **144** under CuAAC-reaction conditions. After preparative HPLC-chromatography, the target product **145** was isolated in 39% yield. An analysis of the cytotoxic activity of macrocycle **145** showed that the toxicity to MA 148 and HUVEC cancer cells doubled compared to calixarene 0118 (fig. 31).

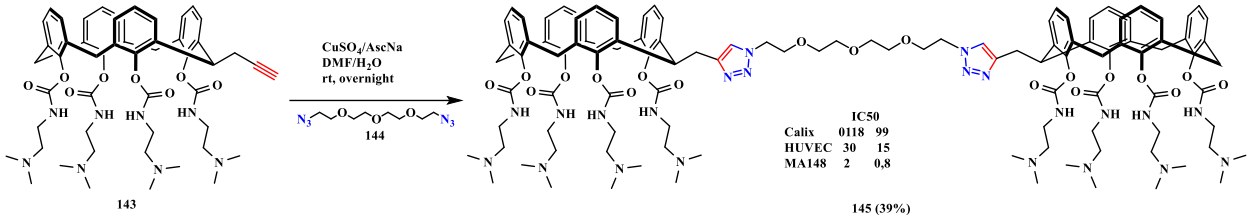


Fig. 31. Cytotoxic bis-calixarene **145** and its IC_{50} values compared to calixarene 0118

The Vatsuro`s scientific group [29] proposed a method for obtaining calix[4]semitubes based on azide and alkynyl derivatives, substituted at the lower rim. Macrocycle **146** was introduced into the CuAAC reaction with macrocycle **67** in the *1,3-alternate* stereoisomeric form in a toluene. Triethylamine was used as a base, and copper iodide (I) acted as a catalyst. The calix[4]semitube **147** was formed in 38% yield. Vatsuro`s scientific group also formulated an approach to obtain longer semitubes with various substituents: use the reaction between macrocycle **148** with trimethysilyl protection of the terminal triple bond and macrocycle **149** as the key synthon and de-silylation of **150** as the intermediate step (fig. 32). Thus, semitube **151** can be further used in reactions with other calixarenes. Later on, the authors demonstrated the possibility of using calix[4]semitubes as a switchable complexing agents for silver ions [104].

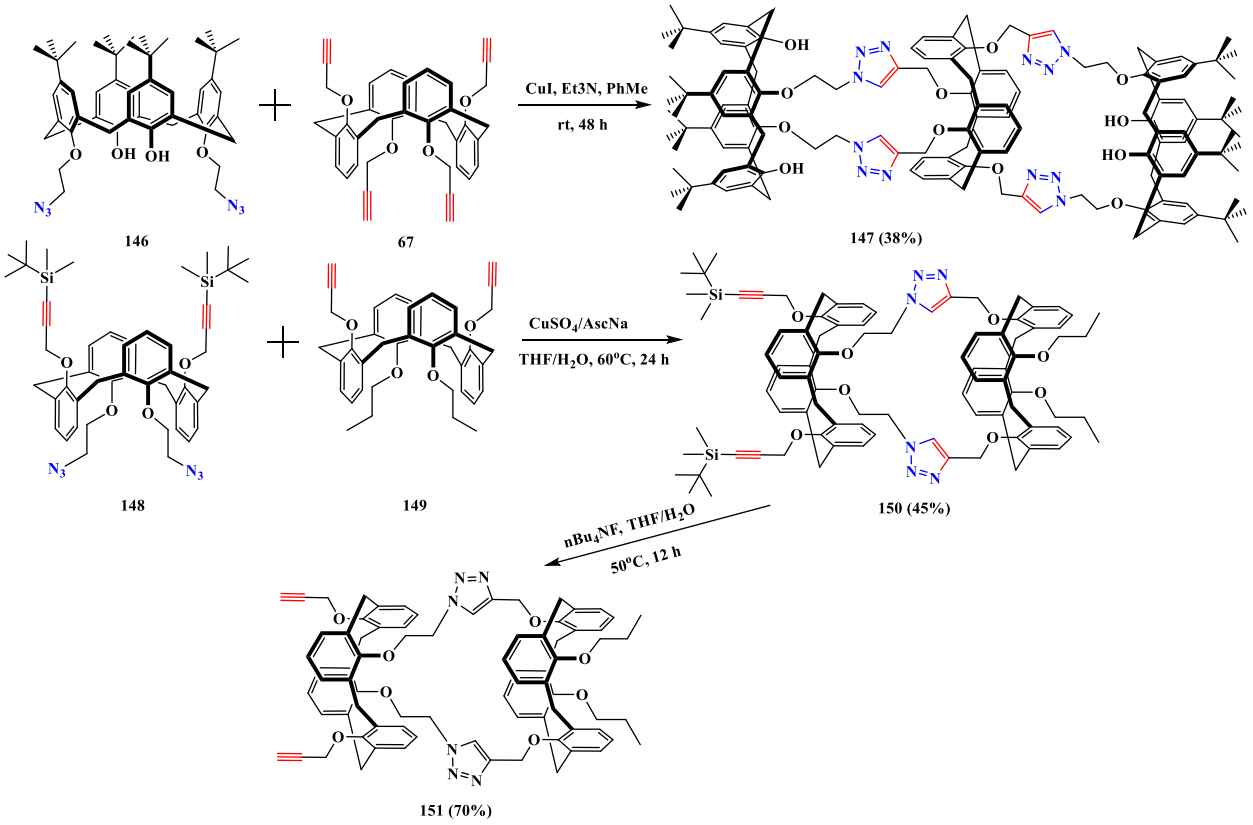


Fig. 32. Synthetic route for obtaining calix[4]semitubes

Thus, the CuAAC- reaction approach is a powerful tool for constructing multiple complex compounds consisting of several calixarene molecules. To date, this area of publications is scarce, which undoubtedly indicates the relevance of further studies of multicalixarenes and the study of their properties.

3.3 Amphiphilic calixtriazoles

The key advantage of the CuAAC reaction is its exceptional tolerance to introduced functional groups, allowing the direct introduction of even ionized fragments without the use of protective groups, which makes it possible to synthesize libraries of various compounds, including amphiphilic ones, simply by changing the azide or alkyne-containing structural modules [105, 106]. This approach can be extended to molecules of (thia)calix[4]arenes due to the possibility of easy and selective modification of their structures.

One of the first works where a modular approach was applied and a wide series of amphiphilic calix[4]arenes was obtained was the work of British scientists led by Sharma [73]. Thus, using the available di- and tetrachloromethyl derivatives of calix[4]arene, by reaction with sodium azide under microwave heating, di- and tetraazides **152**,**153** were obtained in almost quantitative yields in 20 minutes. The resulting azides were used in the CuAAC reaction with propargylated amino acids, dipeptides, and disaccharides. The reaction was also carried out under microwave heating to give final products **154-163** in moderate to quantitative yields (fig. 33).

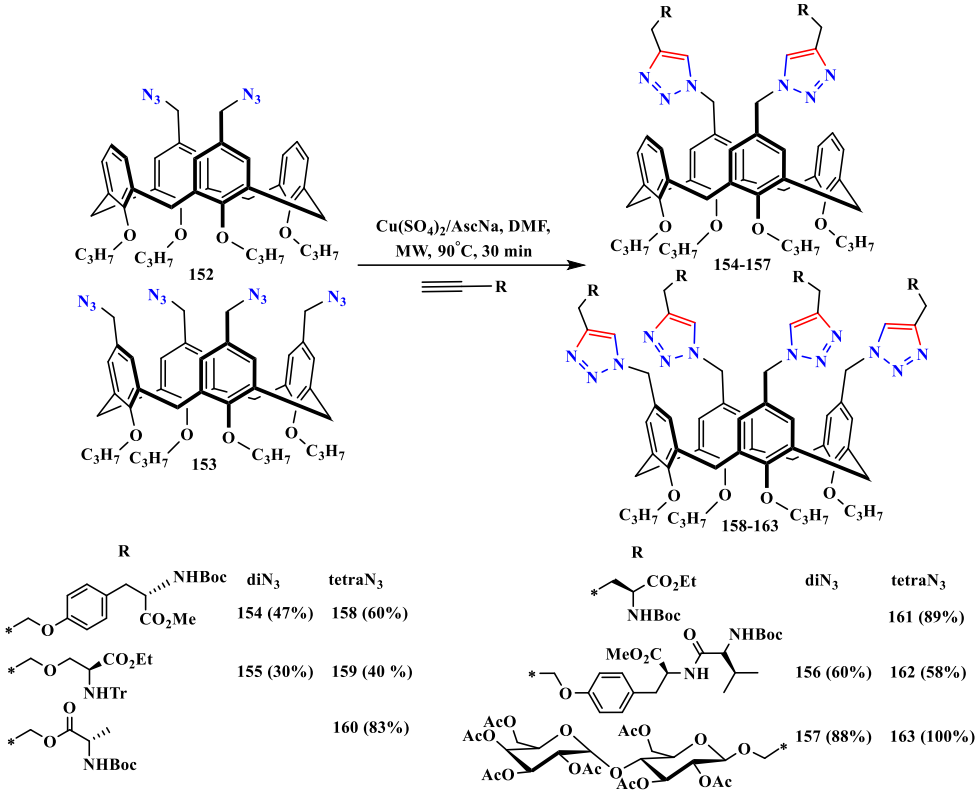


Fig. 33 First amphiphilic calix[4]arenes, synthesized using CuAAC approach

Later, in Shen's group, CuAAC was used for the synthesis of amphiphilic star-like copolymers [107]. For this, two propargyl and methyl acetate fragments were sequentially introduced into the starting *p-tert*-butylcalix[4]arene. Methyl acetate fragments were then reduced to alcohol. The resulting macrocycle **164** (fig. 34) was allowed to polymerize with ε-caprolactone and tin (II) 2-ethylhexanoate as a catalyst, obtaining polymer **165** with a polymerization degree from 11 to 40. Polyoxyethylated fragments containing 25/45 units were introduced into the resulting polymer using CuAAC. The resulting polymer **166** was found to form aggregates in aqueous solutions. The length of the hydroxyethyl fragments showed significant influence on the size of the aggregates. As the content of polyoxyethylated fragments decreased, the size of the aggregates increased from 10 to 30 nm, and further reductions resulted in the formation of vesicles ranging in size from 100 to several hundred nm.

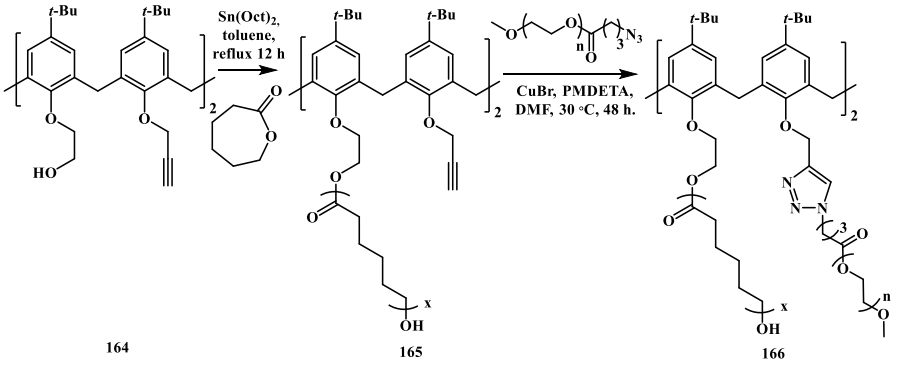


Fig. 34. Polymerizable amphiphiles based on *tert*-butylcalix[4]arene **166**

The Sakurai group uses the CuAAC modular approach extensively in its work to create amphiphiles. Thus, over the past decade [108–114], they have obtained a series of amphiphilic triazoles containing cationic, zwitterionic, and nonionic head groups (fig. 35). An azidomethyl-containing calix[4]arenes **153,167,168** in a *cone* configuration with various alkyl substituents were used as the base molecular platform. The target amphiphilic macrocycles **169-176** were obtained in high and even quantitative yields. Much work has been done to study the physicochemical properties of the resulting triazoles. For example, it was shown that calix[4]arene **169** forms micelles in the acidic pH region, and with an increase in pH due to deprotonation, the micelles transform into cylindrical structures, and in the case of a macrocycle with longer alkyl substituents (hexyl) the transition from micelles to vesicles occurs. The more lyophilic calixarene with nonyl substituents immediately formed cylinders at low pH values. Calix[4]arene **170** containing cysteine fragments was used as a template for the synthesis of 2 nm monomodal gold nanoparticles, which exactly corresponds to the size between adjacent cysteine fragments attached to the calix[4]arene platform. The authors used the $CuSO_4$/sodium ascorbate system in DMF (fig. 11) to introduce glutamic acid residues into the structure of macrocycle **165**. After the removal of the *tert*-butyl and *Boc*-protecting groups, the aggregation properties of obtained calixarene **171** were studied. Thus, at different pH, a morphological transition from spherical to cylindrical conformation and vice versa took place. This opens up the possibility of controlling and configuring the packaging parameters of such systems and using them to create a new class of smart materials. Calix[4]arenes **172** and **173** containing a choline phosphate group were able to form monodisperse micelles with diameters of 1.9 and 26 nm, respectively. Moreover, mixed micelles based on macrocycles and phospholipid DOPC were actively taken up by cells through endocytosis, which is a great advantage in the development of drug delivery vehicles. A unique feature of macrocycles **174** and **175** with polyethylene glycol fragments to form so-called Platonic micelles was shown. For example, macrocycle **174** formed only dodecamer particles, while macrocycle **175** with bulkier polyethylene glycol fragments formed octamer particles. It is noteworthy that macrocycle **176** with the bulkiest polyethylene glycol fragments was generally unable to form stable micelles due to a strong shift in the hydrophilic-lipophilic balance.

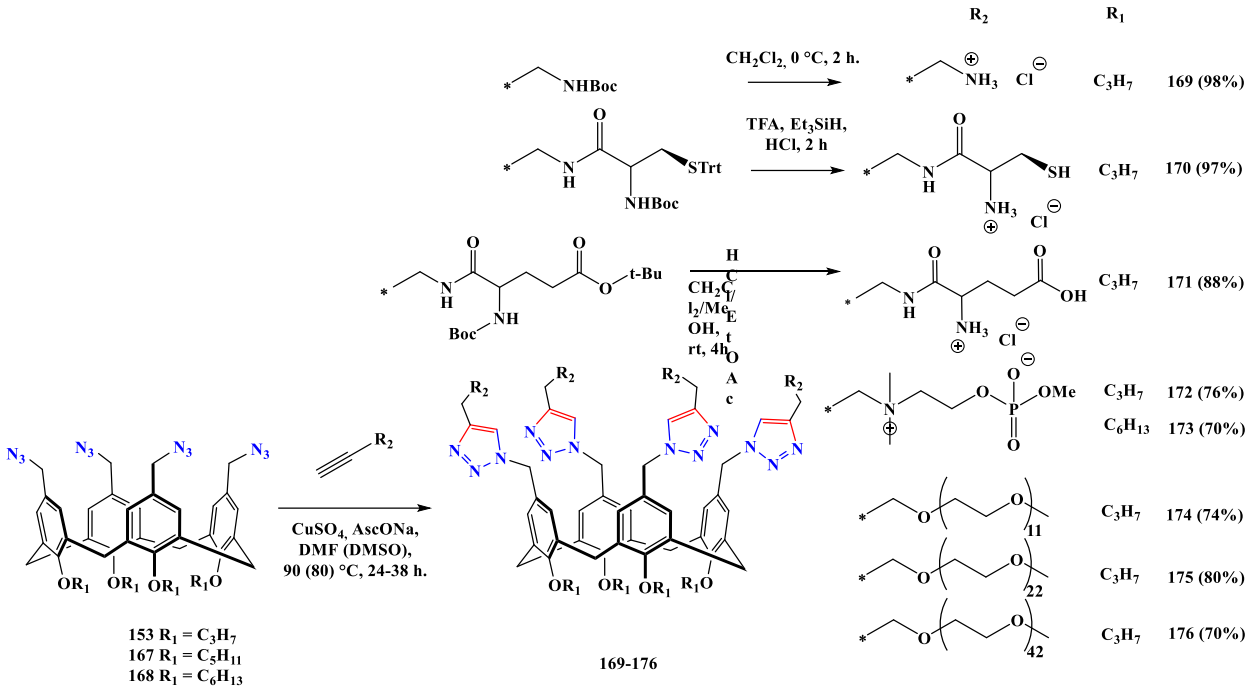
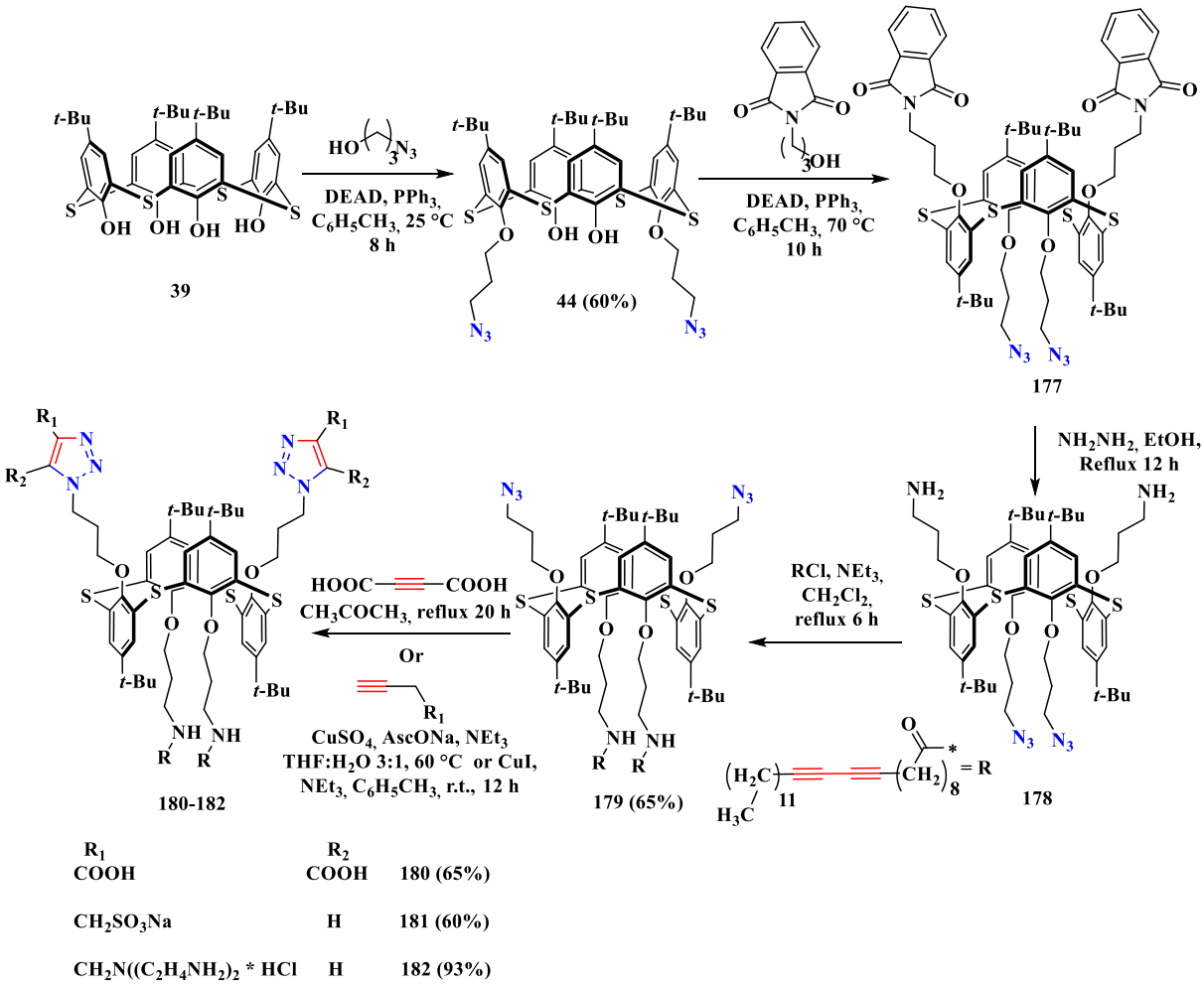


Fig. 35. Sakurai`s amphiphilic calix[4]arenes

In our research group, thiacalix[4]arene derivatives containing photopolymerizable 10,12-pentacosadiinamide fragments were obtained [65, 115]. For this purpose, propylazide and propylphthalimide fragments were sequentially introduced into the starting *p-tert*-butylthiacalix[4]arene. Resulting tetra-substituted macrocycle **177** was subjected to hydrazinolysis and acylation with 10,12-pentacosadiinoyl chloride to give azide **179** in 65% yield (fig. 36). Carboxyl, sulfonate [115], and diethylenetriamine [116] groups were introduced into the obtained azide using AAC reaction. It was shown that the incorporation of macrocycles **180** and **181** into vesicles formed by 10,12-pentacosadiic acid led to the formation of stable submicron particles about 300 nm in size [115]. An increase in the content of calixarene in vesicles caused a slight decrease in the degree of polymerization of 10,12-pentacosadiic acid, but the addition of calixarene led to the appearance of a colorimetric response of photopolymerized vesicles to lanthanide ions with a detection limit of up to 8 mM. It was shown that the colorimetric response in the series of lanthanide ions depends on the ionic radius, and the largest response was found for the La(III) ion.



R_1	R_2	
COOH	COOH	180 (65%)
CH_2SO_3Na	H	181 (60%)
$CH_2N((C_2H_4NH_2)_2$ * HCl	H	182 (93%)

Fig. 36. Synthetic route for diacetylene-containing thiacalix[4]arene amphiphiles

Amphiphilic triazole macrocycles were used as micellar medium for Suzuki coupling reaction in water. For their synthesis, carboxyl fragments were introduced to the upper rim of the macrocycles **21,22,183** by AAC reaction with acetylenedicarboxylic acid. Upon reflux in acetone for 12 hours, target products **184**–**186** were formed in yields from 86 to 92% (fig. 37) [19]. For the octacarboxy-containing calix[4]arenes **184-186**, it was found that the values of the critical aggregation concentration decrease with increasing lipophilicity. The resulting macrocycles were used as a micellar medium for the Suzuki cross-coupling reaction in water between phenylboronic acid and *p*-halobenzenes with various acceptor groups. The best results were shown by the most lipophilic macrocycle **186**.

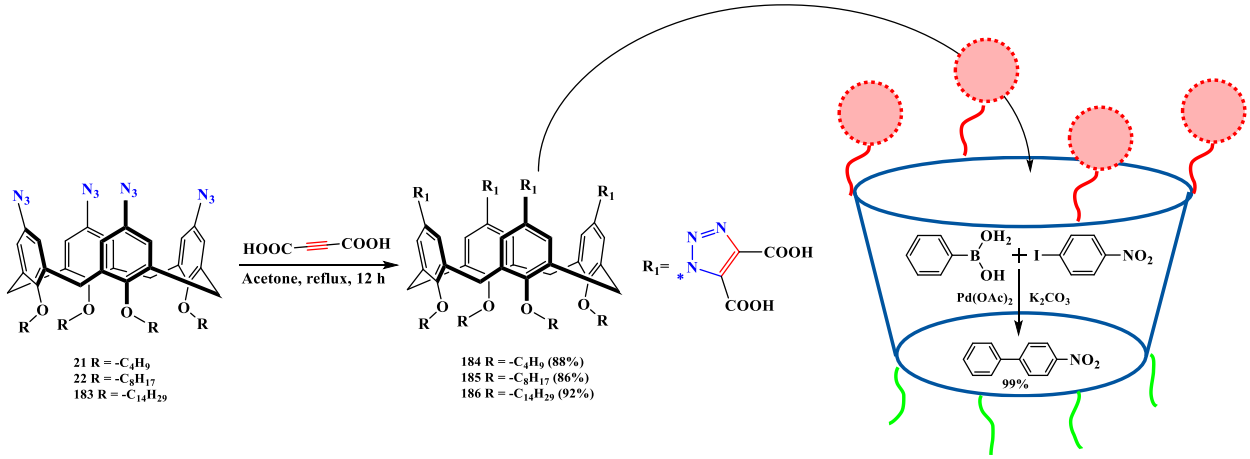


Fig. 37. Synthesis of octacarboxy-containing macrocycles and their use as micellar medium for Suzuki cross-coupling reaction

Recently, we proposed to use amphiphilic thiacalix[4]arenes as a medium for a model reaction of phenylboronic acid oxidation, thereby combining two approaches of micellar and photoredox catalysis [117]. For this purpose, a fluorescein derivative with an oligoethylene glycol fragment **187** was introduced into different macrocycles under the CuAAC reaction conditions (fig. 38, by way of example **42**). The photocatalytic activity of obtained amphiphiles was tested. The best results in *ipso*-hydroxylation of phenylboronic acid were demonstrated by macrocycle **188** with tetradecyl alkyl groups - the conversion of the target phenol was 91%. It has also been shown that the addition of the low molecular weight surfactant Triton-X100 increases the catalytic activity of macrocycle **188,** thus showing the importance of a combination of micellar and photoredox catalysis.

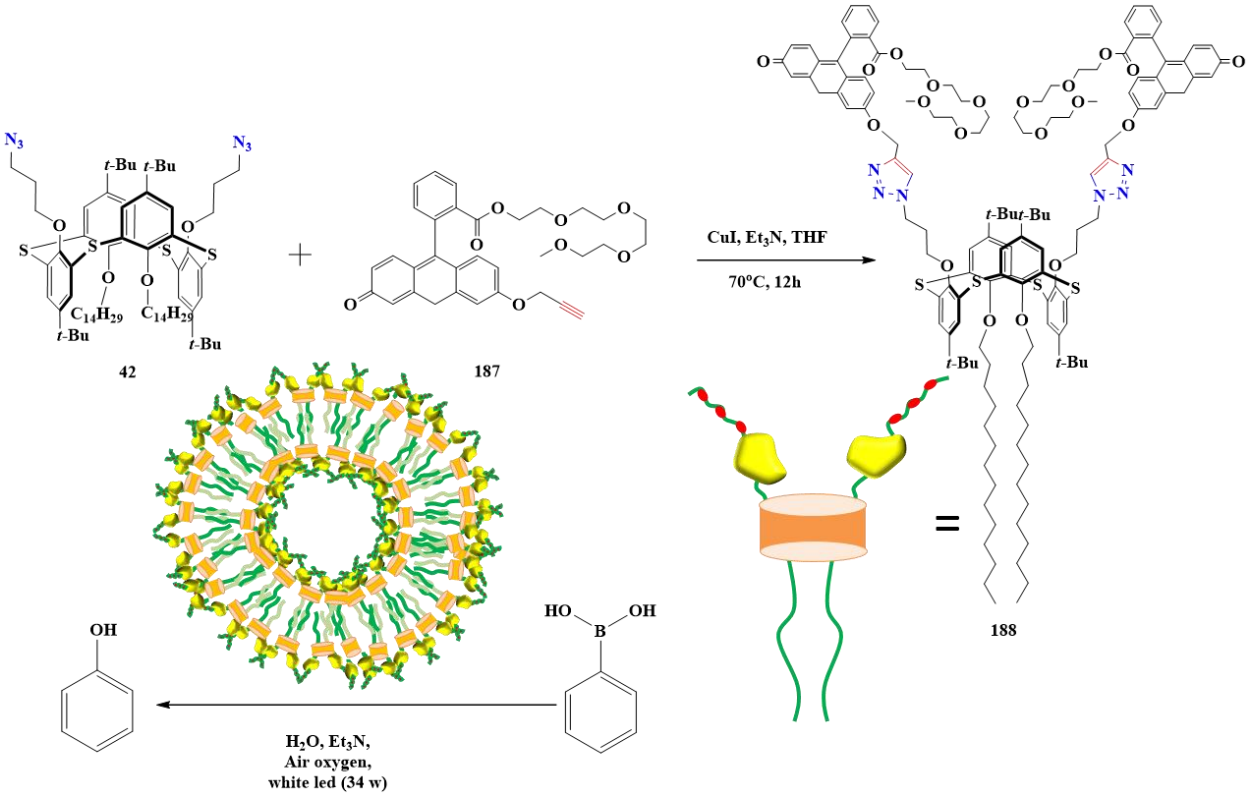


Fig. 38. Synthesis and photocatalytic activity of fluorescein containing macrocycle **188**

Thus, the scope of application of amphiphilic macrocycles is truly enormous. In this regard, the click chemistry approach, which involves the modular construction of a target molecule from separate pre-prepared fragments, opens up great opportunities for rapid variation of functional polar groups, hydrophobic fragments, and, by changing the configuration of the macrocyclic platform, directly influences the geometry of the final amphiphile.

3.4 Calixtriazoles for bioapplications

Today, there is great interest in developing methods of drug delivery and cancer treatment. Macrocyclic structures can be used for these purposes. The click chemistry approach makes it possible to obtain systems that can be used in cell imaging [118, 119] capable of exhibiting antibacterial [120] and cytotoxic activity [121], as well as capable of binding DNA molecules to create transfecting agents [122].

As it is known, guanidine-containing compounds are able to bind negatively charged molecules due to the presence of a positive charged nitrogen. This fact has been used by many researchers to create selective sensors for many biomolecules, including DNA [123]. In addition, guanidine derivatives often have low overall toxicity, while exhibiting cytotoxic properties to cancer cells [124], which leads to the widespread use of such compounds in biomedicine and in the creation of antibacterial drugs [125]. Thus, Sansone's group used [126] the CuAAC reaction to introduce guanidinium fragments on the upper rim of calix[4]arene using tetraazidomethyl-containing calix[4]arene **168**. Macrocycle **189,** containing four guanidinium fragments, was obtained quantitatively (fig. 39). The authors compared the efficiency of DNA transfection with macrocycle **189** compared to the analog **190** containing an amide instead of a triazole spacer and found that the compound with the amide spacer was slightly more efficient. At the same time, the efficiency of transfection of macrocycles with amide/triazole spacers turned out to be significantly higher than for calix[4]arenes containing four guanidine fragments directly linked to aromatic

rings. The authors explain the increase in transfection efficiency by the presence of additional nitrogen atoms, which, being reversibly protonated, impart a certain buffering capacity to the macrocycle and its complex with DNA, thereby facilitating the release of endosomes through the "proton sponge" mechanism.

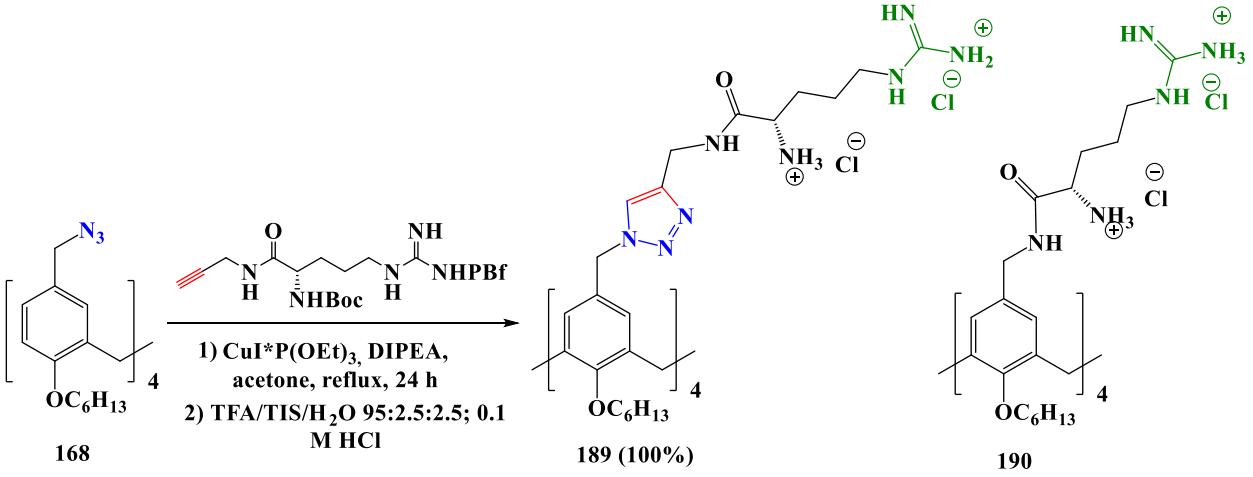


Fig. 39. Guanidine containing macrocycles capable of transfect DNA through cell lines

In the work of Samanta *et al* [122], the authors used CuAAC to modify the dipropargyl macrocycle **191** (fig. 40) with propylguanidinium linkers. A coumarin derivative **193** was introduced into the lower rim by an acylation reaction, and the functional derivative **194** was obtained after the Boc-removal. The resulting bimodal cationic calix[4]arene effectively binds plasmid DNA pBR322 (a clone of the *E. coli* vector). In addition, the authors found efficient transfection of pCMV-tdTomato-N1 plasmid DNA through the MCF-7 (breast adenocarcinoma) and SH-SY5Y (metastatic bone tumor) cell lines without the addition of helping reagents (dioleoylphosphatidylethanolamine - DOPE *etc*.).

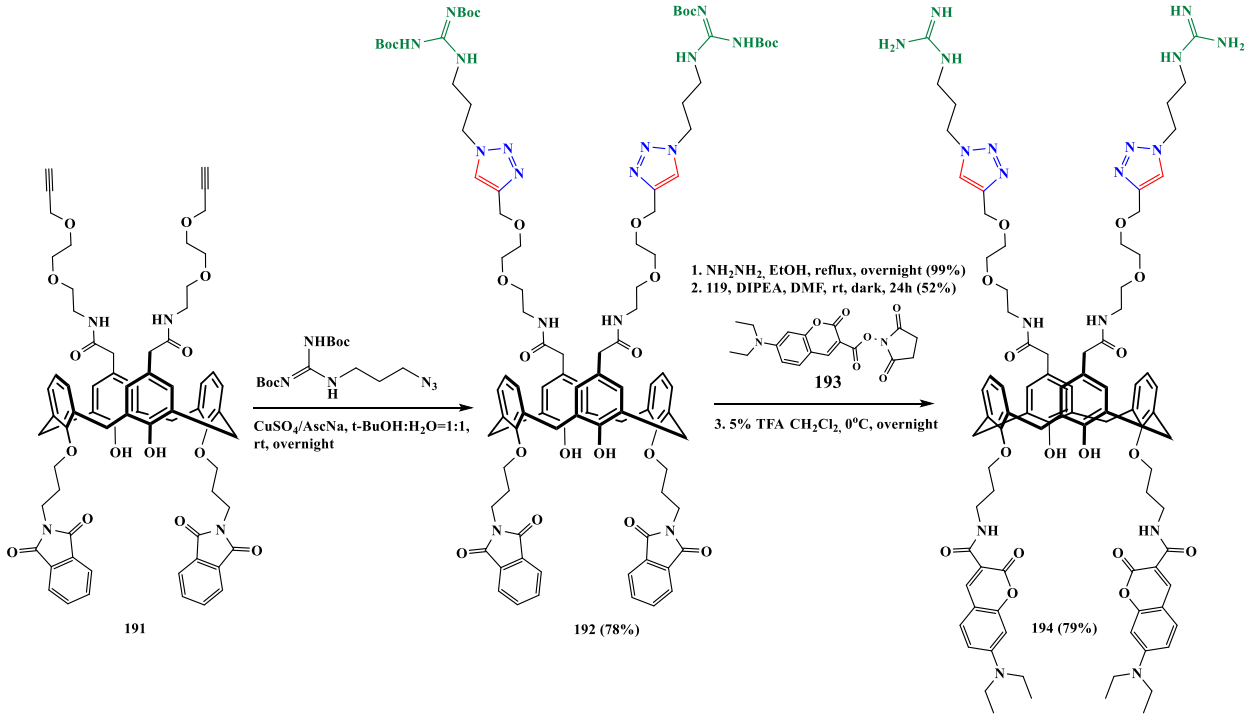


Fig. 40. Synthesis of efficient DNA transfector **194**

Creation of triazole macrocycles capable of binding various drugs was shown by the authors of [127]. Target macrocycle **196** (fig. 41) was obtained by CuAAC reaction of dipropargyl calix[4]arene **12** with azide-containing thiazole **195** in DMF for 12 hours. Using UV-visible spectroscopy, it was shown that the resulting supramolecule **196** perfectly binds the antibiotic cefuroxime in the presence of other drugs in aqueous solutions in a wide pH range of 2-12. In addition, the efficiency of the process is maintained in human plasma and tap water.

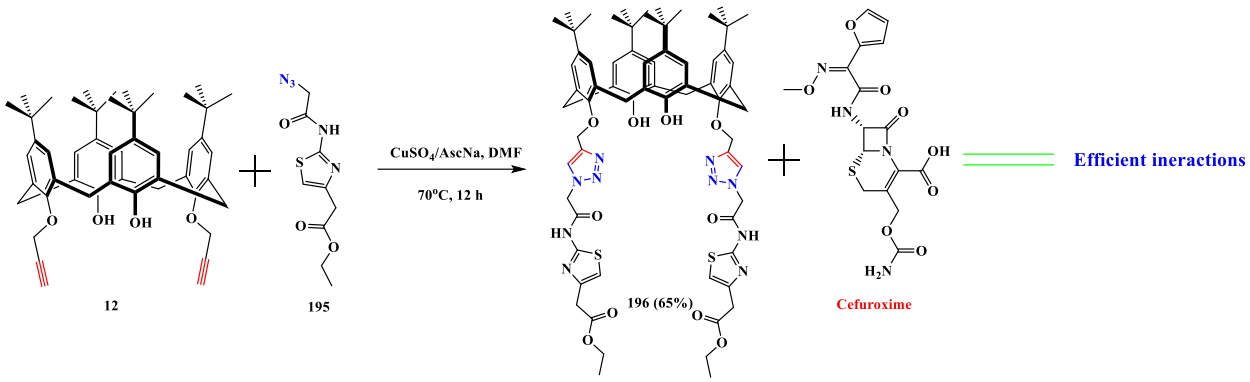


Fig. 41. Synthesis of macrocycle **196** with binding abilities toward cefuroxime

A lot of work on the synthesis of new calixarene-cyclodextrin copolymers by click chemistry approach was carried out by the scientific group of Lo Meo [128]. Authors studied the possibilities of calixarene-cyclodextrin copolymers post-modification [129] and use as pH-dependent nanosponges [130], which can be used as a transport for the delivery of tetracycline molecules [131]. Nanosponges were designed (fig. 42) using tetrapropargyl substituted macrocycle **14** and azide **197** obtained from cyclodextrin. Polymerization was carried out under CuAAC conditions in dimethylsulfoxide (DMSO) at 70°C for 18 h. With a twofold excess of the azide component, copolymer **198** was formed and then further subjected to reduction under Staudinger conditions with the formation of amine **199**. With a twofold excess of calixarene **14**, copolymer **200** was formed, which further subjected to "click"-reaction with ethyl 3-azidopropanoate, followed by alkaline hydrolysis using NaOH (1M) in methanol. A sequestration test at pH equal to 4.4 and 6.7 have shown that the interaction between tetracycline and compounds **198**-**201** may be significantly affected by pH variations and is highly dependent on electrostatic interactions between the guest and the copolymer matrix. Moreover, the materials proved to be perfectly treatable under sterile conditions and showed no biocidal activity. Also, the authors evaluated the antibacterial activity of tetracycline-**198** and tetracycline-**199** composites relative to some Gram-positive and negative bacteria. Obtained systems in some cases showed higher values of IC_{50} relative to free tetracycline.

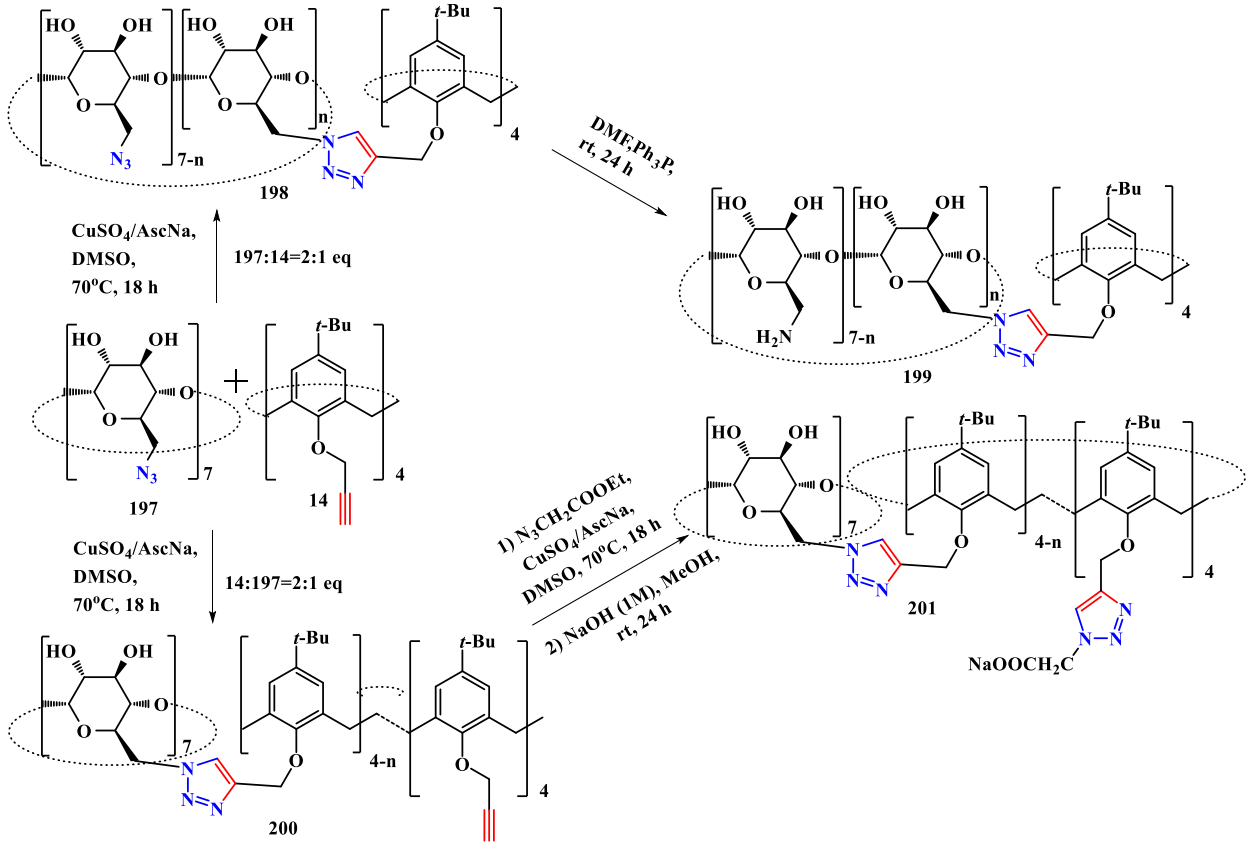


Fig. 42. Calix[4]arene-cyclodextrine copolymers used as nanosponges for delivery of tetracycline

The Agrahri`s scientific group used CuAAC approach to design dendrimer with benzotriazolyl moieties based on a calixarene platform **203** (fig. 43). Zero-generation dendrimer **202** was also synthesized. Both compounds exhibited dose-dependent biofilm inhibition against the methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus, E.Coli, Klebsiella pneumonia, Pseudomonas aeruginosa* bacteria. Calix[4]arene **202** showed the most effective antibacterial and anti-biofilm activity against drug-resistant and slime-forming organisms, while showing no cytotoxicity to mammalian cell lines [44].

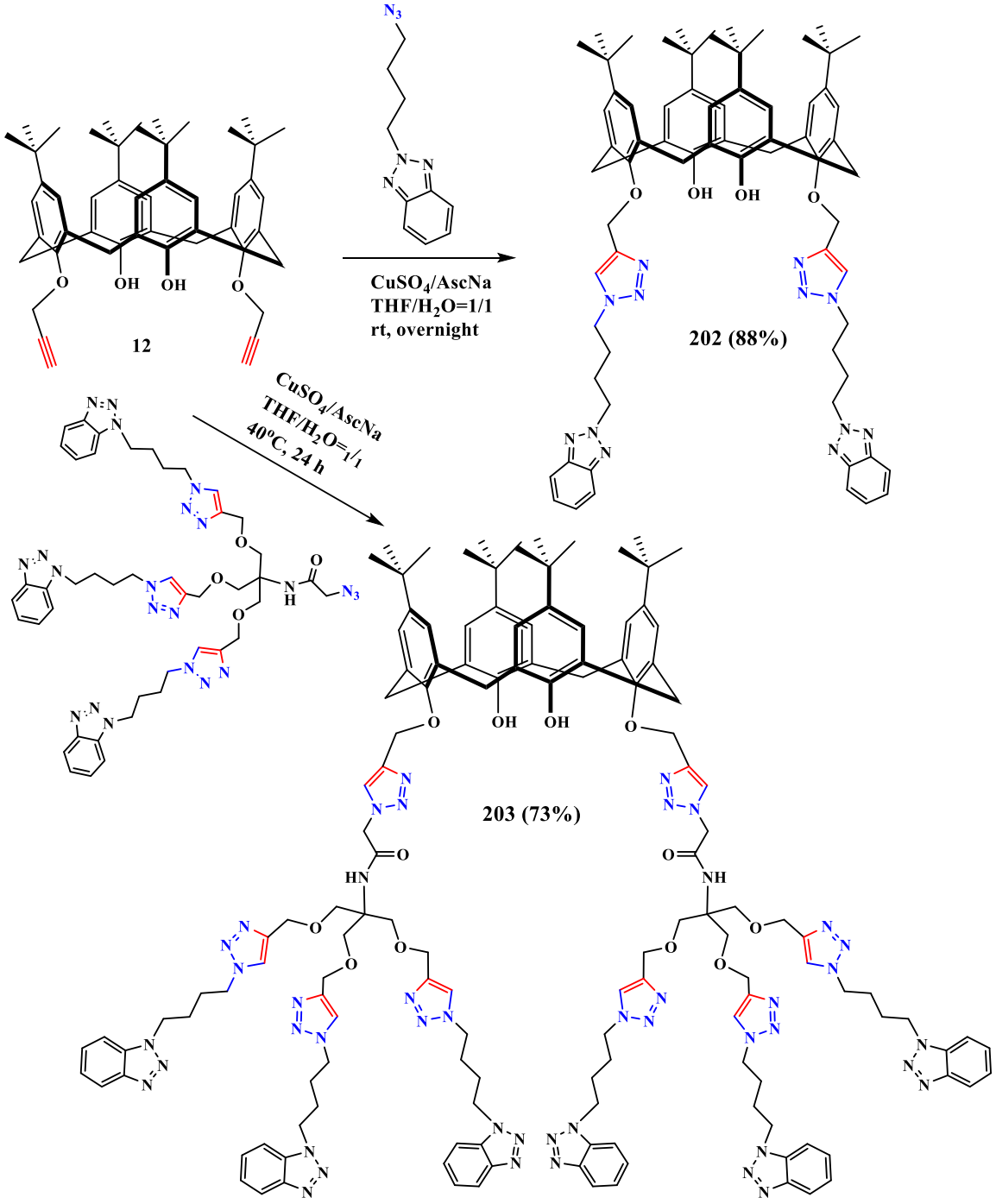


Fig. 43. Potential anti-bacterial agent **202** and triazole-dendrimer **203** based on calix[4]arene

The CuAAC reaction can also be used to modify calix[4]arenes with carbohydrate fragments. The authors of [38] introduced C-glycosidic fragments with various substituents **204**–**206** into the structure of macrocycle **5** containing alkynyl groups (Fig. 44). The authors used CuI as the catalysts and *N,N*-diisopropyl-*N*-ethylamine as the base. The scientific group of Galante used microwave heating to synthesize carbohydrate derivatives from alkynyl calixarenes **14** and **207** in the *cone* and *partial cone* configuration and azide **208** with acylated lactose ester (Ac Gal β (1-4) Glc) fragments. Subsequent hydrolysis of ester groups made it possible to obtain tetrasubstituted glycoclusters **211** and **212**, shown in figure 34 [74].

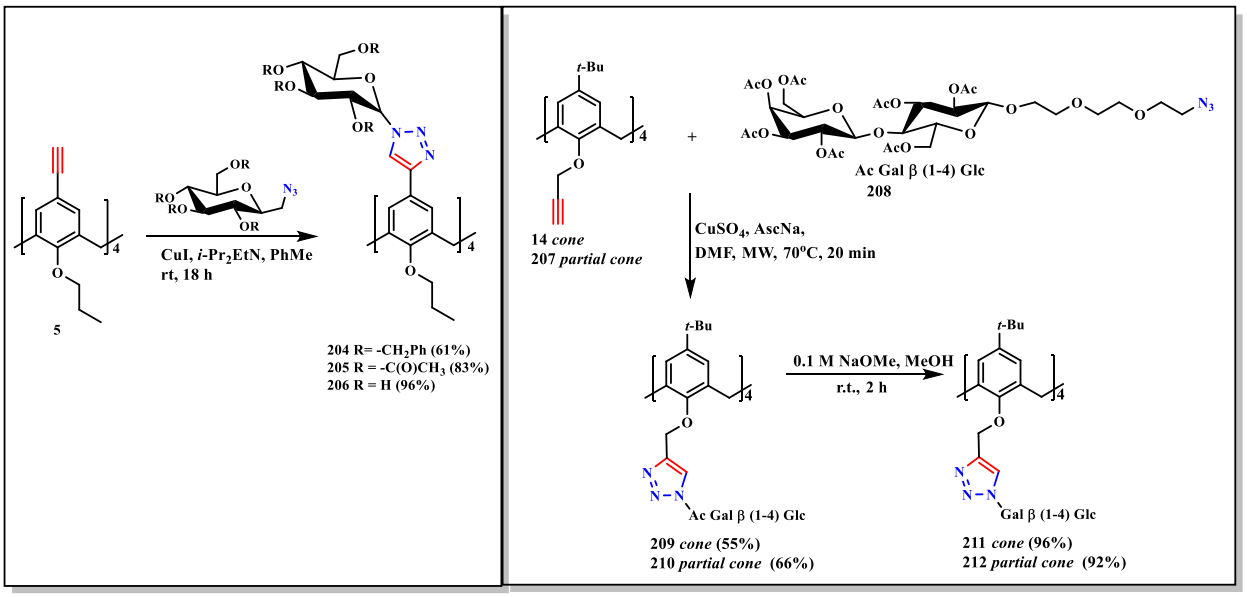


Fig. 44. Methods of introducing carbohydrates into macrocyclic structure using CuAAC reaction

Work of Moni *et al* [132] can serve as another example of the synthesis of glycoclusters on the calixarene platform. The authors obtained oligonucleotide derivatives based on macrocycle **215** (fig. 45) with 4 (**217a**) and 8 (**217b**) galactose fragments, respectively, which were further studied for possible binding by lectins of different structures - PA-IL (Pseudomonas aeruginosa lectin) and RCA 120 (ricinus communis agglutinin). Selective recognition was observed for RCA 120, while PA-IL showed no response.

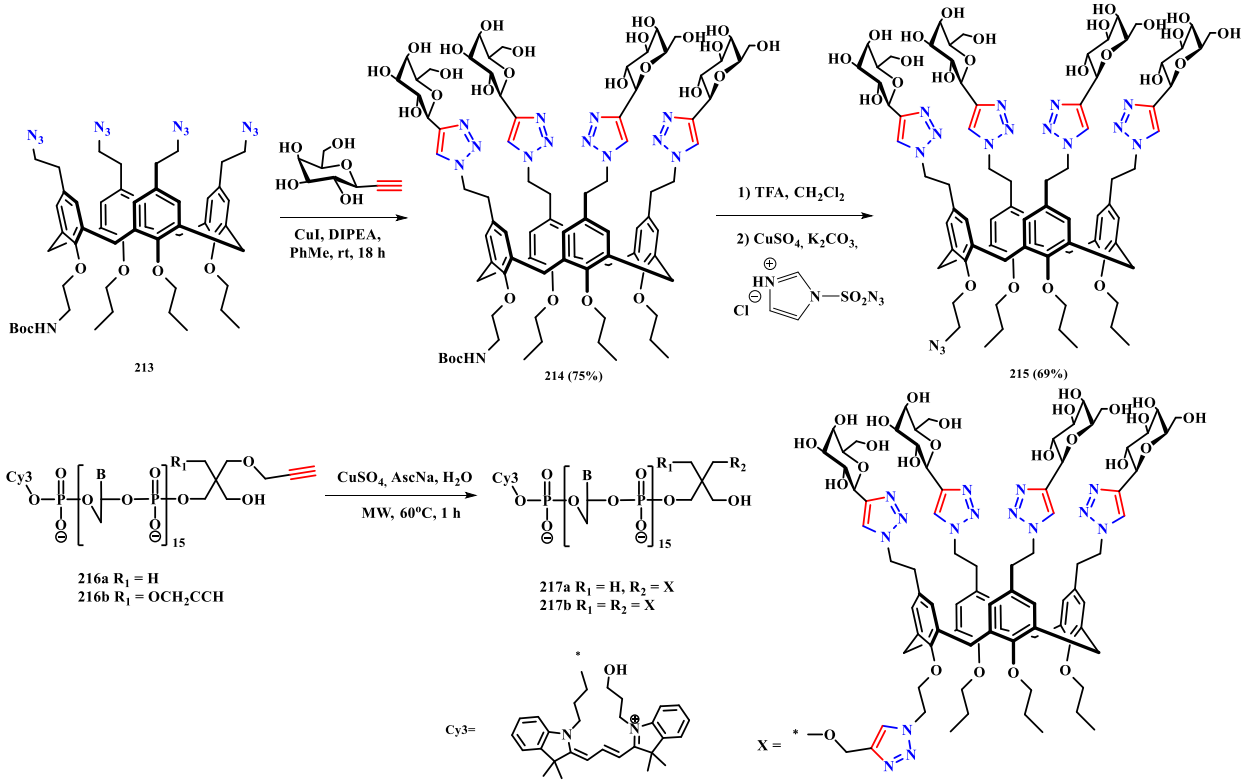


Fig. 45. Calix[4]arene glycoclusters studied for possible binding by lectins

Recently, Konovalinkova *et al.* [133] reported the synthesis of glycocalixarenes **220-223a,b** (fig. 46) in four stereoisomeric forms, where the lactosyl fragment is directly linked to the triazole linker as well as macrocycles **224a,b** and **215a,b**, where the functional fragment is linked to the triethylene glycol and propyltriazole linkers, respectively. The authors determined the affinity of the prepared compounds to a library of human galectins.

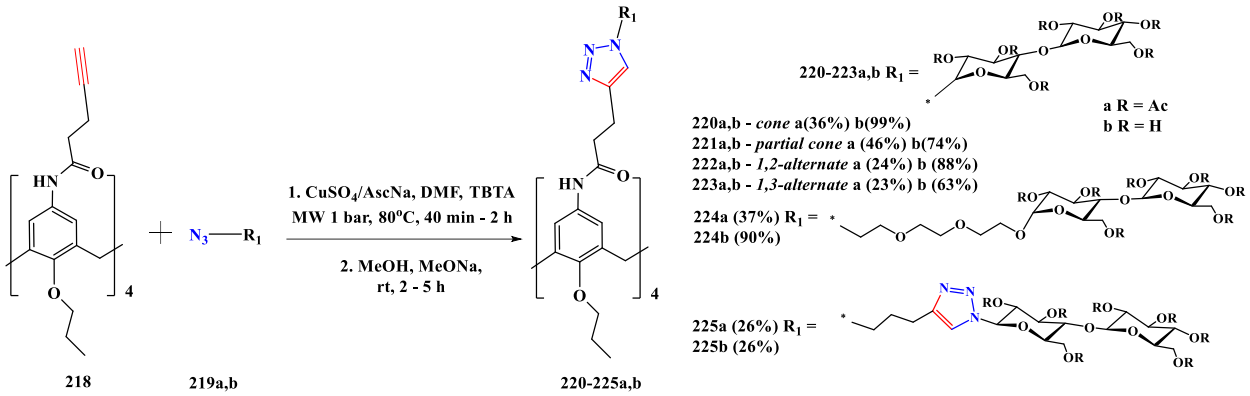


Fig. 46.Synthesis of glycocalixarenes by Konovalinkova *et al.*

The use of CuAAC reaction to obtain calix[4]arenes, capable for cell imaging is presented in Ramachandran *et al*. work [119]. To obtain the target product (fig. 47), dipropargyl macrocycle **12** was introduced into a "click"-reaction with 4-azido-2,2`-bipyridyl **226**. After column chromatography, ligand **227** was isolated in 41% yield. Next, the complex formation reaction was carried out by reflux of **227** in methanol with *cis*-dichlorobis(bipyridine)ruthenium(II) (cis-$Ru(bpy)_2Cl_2$). The resulting complex showed selective binding of copper (II) ions in the presence of a wide range of other metals, forming a complex in 1:1 stoichiometry. The resulting copper-**228** complex showed excellent interaction with sulfide anions in the presence of other anions and can be used as a turn-on luminescent sensor. In addition, the cytotoxic properties of the ruthenium complex were studied, where **228** showed the best results in IC_{50} values towards adenocarcinomic human alveolar basal epithelial cells (A549 cells) compared to cisplatin and ruthenium polypyridine. Furthermore, **228** have been used in fluorescence imaging studies, where the apoptosis and necrosis cells can be clearly differentiated from the control cells using cellular uptake.

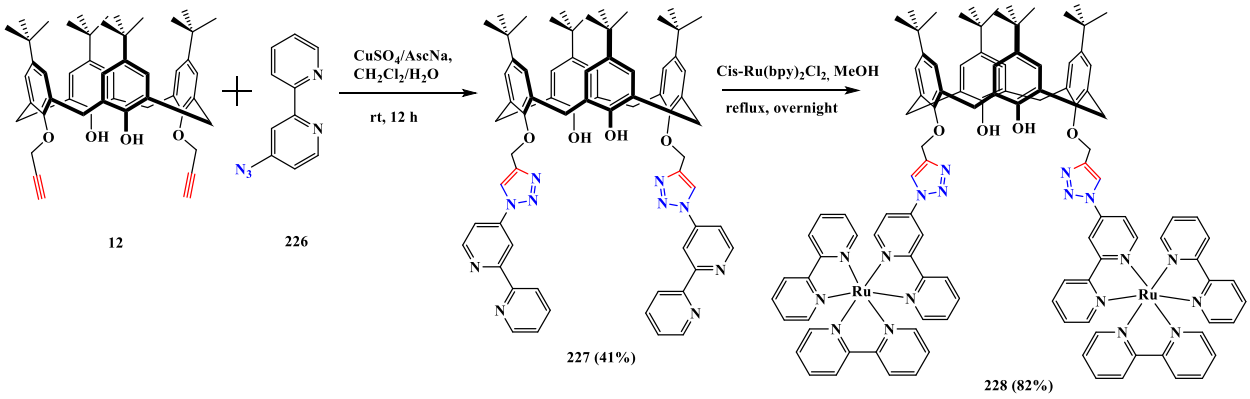


Fig. 47. Synthesis of complex **228** for cell imaging

Our scientific group proposed a method for the synthesis of amines and ammonium salts on the lower rim of the thiacalixarene platform using the CuAAC reaction. To obtain both poly- and mono-cationic derivatives of thiacalix[4]arene, CuAAC reactions with alkynes of various structures were carried out. Reaction of compounds **40-42** with *N*,*N*-bis[2-(*tert*-butylcarbonylamino)ethyl]-propargylamine (fig. 48) in the presence of triethylamine and copper iodide in toluene gave target products **230-232** in good yields. Using the fluorescent ethidium bromide displacement method, it was found that water-soluble compounds **230-232** bind calf thymus DNA (DNA-CT), and macrocycle **232** with the lipophilic tetradecyl fragments shows the best efficiency. It was found that macrocycles are able to condense DNA molecules: a 5-fold decrease in size is observed upon elongation of the alkyl chain [23]. *N*-propargyl-*N*,*N*,*N*-triethylammonium bromide was reacted under similar conditions (fig. 48) to give ammonium salts **233-235**, which are capable of interacting with bovine serum albumin (BSA) to form a complex in a 1:1 stoichiometry. Again, the most lipophilic calix[4]arene **235** showed the best efficiency, due to interaction with the hydrophilic surface of BSA through electrostatic forces and with the hydrophobic binding pocket of BSA through hydrophobic interactions [134].

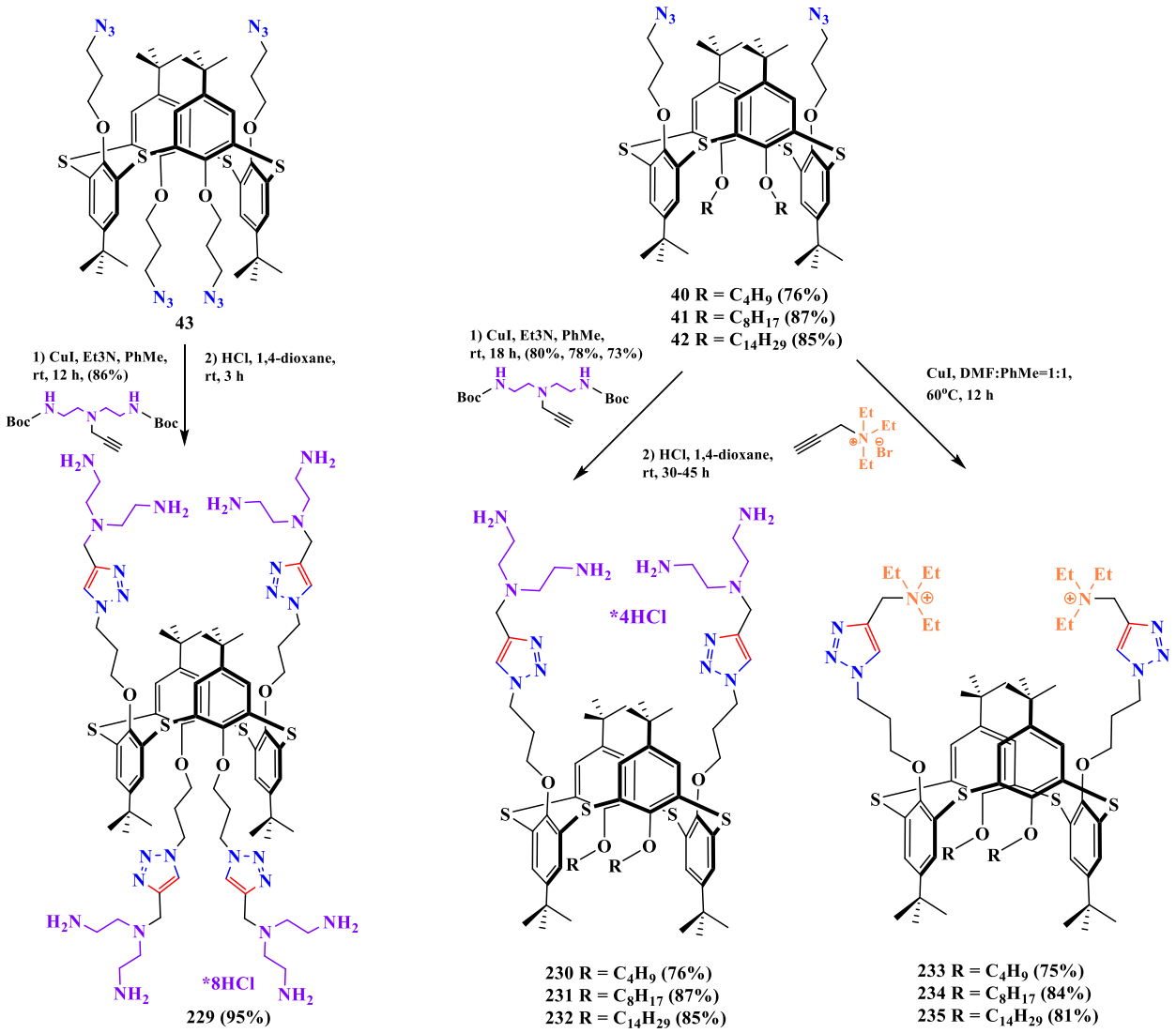
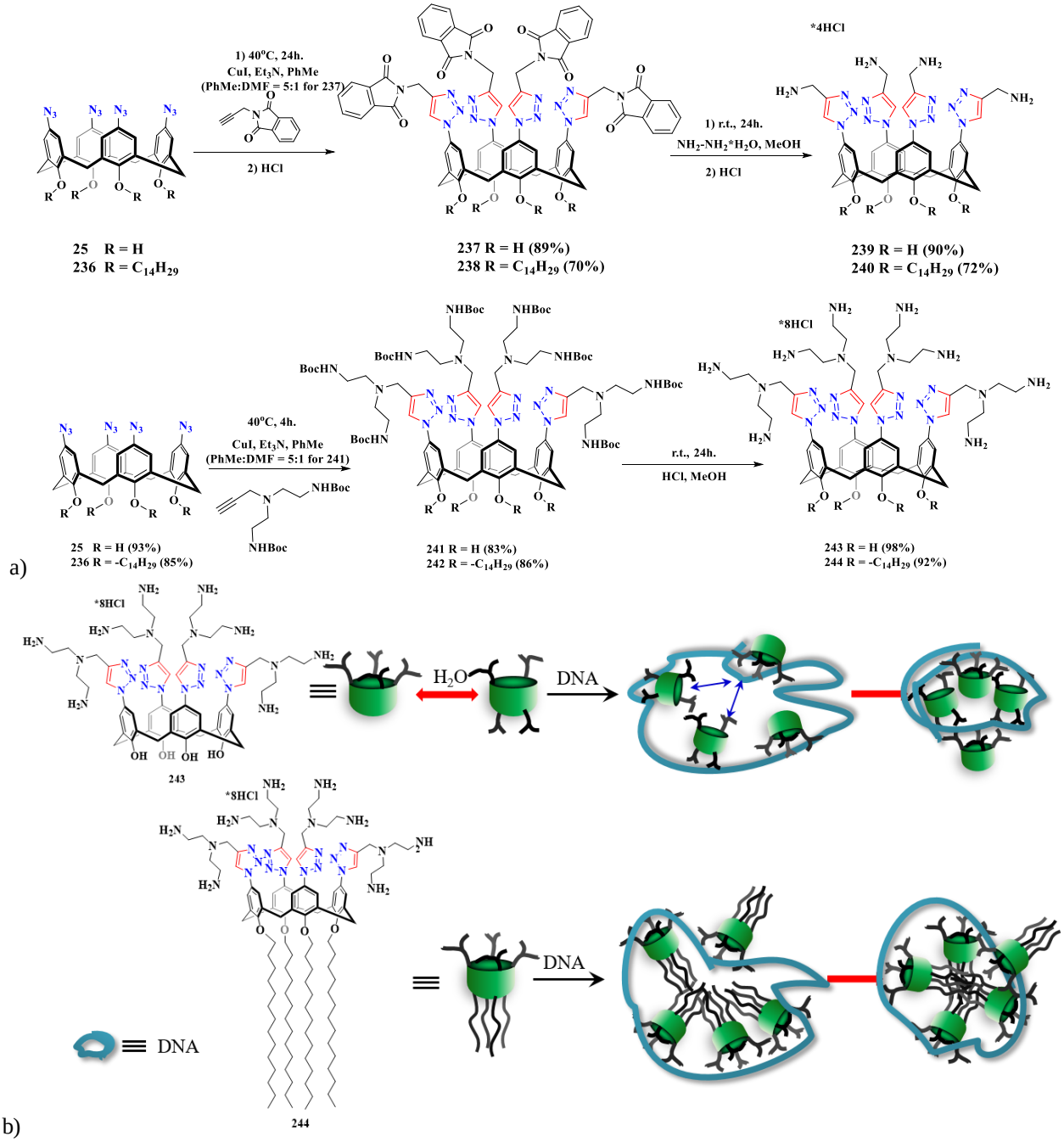


Fig. 48. CuAAC-reaction for the synthesis of amines and ammonium salts using thiacalix[4]arene *1,3-alternate*

In 2017 [135], the possibility of using macrocycles **233-235** together with eosin Y as a fluorescent sensor for detection of various surfactants was demonstrated. The release of the dye occurs when interacting with sodium lauryl/laureth sulfate. Recently [68] it has been proposed to use a similar synthetic strategy to prepare triazole-containing polycationic macrocycle **229**, which demonstrated a two orders of magnitude increase in the binding constant of DNA-CT compared to diethylene triamine - the presence of four functional fragments on a single platform promotes multivalent interactions.

Our scientific group also obtained polydiacetylene containing macrocycle **182** with the same diethylene triamine polar groups (fig. 36). Calix[4]arene **182** was able to form submicron particles with a size of 200 nm and a surface potential of +43 mV [116]. Using ethidium bromide, it was found that **182** intercalates DNA-CT, forming a lipoplex with a surface potential of -30 mV. The resulting macrocycle was used to synthesize mixed polydiacetylene particles with *N*-(2-aminoethyl)-10,12-pentacosadiinamide as a base lipid. The resulting particles showed a colorimetric response to DNA visible to the naked eye at a DNA-CT concentration of 20 μmol/l.

Based on the azide **25**, mono- **239** [121] and polyamine **243** [58] were synthesized (fig. 49a). Their analogues **240** and **244** with a long tetradecyl alkyl substituent were obtained as well (fig. 49a). Using the ethidium bromide displacement method, it was found that all of the obtained calixarene amines can bind DNA-CT. The best results were found for polyamine macrocycles **243** and **244**. Using CD method, it was found that the DNA structure does not undergo destruction upon interaction with calixarenes. Using DLS and TEM methods it was found that the macrocycle with free OH groups **243** condenses DNA into gorgon-like branched structures (fig. 49b), while tetradecyl one **244** interacts more efficiently and forms ordered vesicle-like structures. At the same time, **243** demonstrated less cytotoxicity for HSF cells while maintaining activity against MCF and PC3 cancer cells (fig. 49c).



c)

Compound	IC50		
	Tumor cell lines		Normal cell lines
	MCF7	PC3	HSF
243	3.3	7.4	21.3
244	3.8	19.3	3.8

Fig. 49. a) Synthesis of aminocalix[4]arenes, b) schematic representation of DNA binding motive, c) cytotoxic activity of obtained macrocycles

To summarize, the presented review demonstrates the versatility of the modular click-chemistry approach using the CuAAC reaction for the synthesis of completely different derivatives of calix[4]arenes. The method makes it possible to introduce fragments of different nature, including the formation of bifunctional molecules with the presence of different substituents on the lower/upper rim in one molecule. Given the variety of possibilities for introducing alkynyl or azide fragments into the initial macrocyclic platform, as well as the possibility of obtaining

precursors of the AAC reaction in several stereoisomeric forms, CuAAC can without exaggeration be called the most convenient reaction to obtain a variety of functional macrocyclic derivatives.

Acknowledgments

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Notes and references

1. Neri, P., Sessler, J.L., Wang, M.-X. (Eds.): Calixarenes and Beyond. Cham: Springer International Publishing. (2016). https://doi.org/10.1007/978-3-319-31867-7
2. Morohashi, N., Narumi, F., Iki, N., Hattori, T., Miyano, S.: Thiacalixarenes. Chem. Rev. **106**, 5291–5316 (2006). https://doi.org/10.1021/cr050565j
3. Kumar, S., Chawla, S., Zou, M.C.: Calixarenes based materials for gas sensing applications: a review. J. Incl. Phenom. Macrocycl. Chem. **88**, 129–158 (2017). https://doi.org/10.1007/s10847-017-0728-2
4. Galieva, F., Khalifa, M., Akhmetzyanova, Z., Mironova, D., Burilov, V., Solovieva, S., Antipin, I.; New supramolecular hypoxia-sensitive complexes based on azo-thiacalixarene. Molecules **28**, 466 (2023). https://doi.org/10.3390/molecules28020466
5. Song, M., Sun, Z., Han, C., Tian, D., Li, H., Kim, J.S.: Calixarene-based chemosensors by means of click chemistry. Chem. Asian J. **9**, 2344–2357 (2014). https://doi.org/10.1002/asia.201400024
6. Guo, C., Sedgwick, A. C., Hirao, T., Sessler, J. L.: Supramolecular fluorescent sensors: an historical overview and update. Coord. Chem. Rev. **427**, 213560 (2021). https://doi.org/10.1016/j.ccr.2020.213560
7. Kumar, R., Sharma, A., Singh, H., Suating, P., Kim, H.S., Sunwoo, K., Shim, I., Gibb, B.C., Kim, J.S.: Revisiting fluorescent calixarenes: from molecular sensors to smart materials. Chem. Rev. **119**, 9657–9721 (2019). https://doi.org/10.1021/acs.chemrev.8b00605
8. Santoro, O., Redshaw, C.: Metallocalix[n]arenes in catalysis: a 13-year update. Coord. Chem. Rev. **448**, 214173 (2021). https://doi.org/10.1016/j.ccr.2021.214173
9. Podyachev, S.N., Zairov, R.R., Mustafina, A.R.: 1,3-Diketone calix[4]arene derivatives—a new type of versatile ligands for metal complexes and nanoparticles. Molecules **26**, 1214 (2021). https://doi.org/10.3390/molecules26051214
10. Sachdeva, G., Vaya, D., Srivastava, C.M., Kumar, A., Rawat, V., Singh, M., Verma, M., Rawat, P., Rao, G.K.: Calix[n]arenes and its derivatives as organocatalysts. Coord. Chem. Rev. **472**, 214791 (2022). https://doi.org/10.1016/j.ccr.2022.214791
11. Zuo, M., Velmurugan, K., Wang, K., Tian, X., Hu, X.-Y.: Insight into functionalized-macrocycles-guided supramolecular photocatalysis. Beilstein J. Org. Chem. **17**, 139–155 (2021). https://doi.org/10.3762/bjoc.17.15
12. Pan, Y., Hu, X., Guo, D.: Biomedical applications of calixarenes: state of the art and perspectives. Angew. Chem. Int. Ed. **60**, 2768–2794 (2021). https://doi.org/10.1002/anie.201916380
13. Crowley, P.B.: Protein–calixarene complexation: from recognition to assembly. Acc. Chem. Res. **55**, 2019–2032 (2022). https://doi.org/10.1021/acs.accounts.2c00206
14. Solovieva, S.E., Burilov, V.A., Antipin, I.S.: Thiacalix[4]arene's Lower Rim Derivatives: Synthesis and Supramolecular Properties. Macroheterocycles **10**, 134–146 (2017). https://doi.org/10.6060/mhc170512a
15. Geng, W.-C., Huang, Q., Xu, Z., Wang, R., Guo, D.-S.: Gene delivery based on macrocyclic amphiphiles. Theranostics **9**, 3094–3106 (2019). https://doi.org/10.7150/thno.31914
16. Fan, X., Guo, X.: Development of calixarene-based drug nanocarriers. J. Mol. Liq. **325**, 115246 (2021). https://doi.org/10.1016/j.molliq.2020.115246
17. Krošl, I., Otković, E., Nikšić-Franjić, I., Colasson, B., Reinaud, O., Višnjevac, A., Piantanida, I. Impact of positive charge and ring-size on the interactions of calixarenes with DNA, RNA and nucleotides. New J. Chem. **46**, 6860–6869 (2022). https://doi.org/10.1039/D2NJ00061J
18. Pineda-Castañeda, H.M., Rivera-Monroy, Z.J., Maldonado, M.: Copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction: a powerful tool for functionalizing polyhydroxylated platforms. ACS Omega **8**, 3650–3666 (2023). https://doi.org/10.1021/acsomega.2c06269
19. Fatykhova, G.A., Makarov, E.G., Mironova, D.A., Sultanova, E.D., Burilov, V.A., Solovieva, S.E., Antipin, I.S.: New Amphiphilic calix[4]Arene derivatives with 4,5-dicarboxytriazolyl fragments: synthesis and use in micellar catalysis. Russ. J. Phys. Chem. B **13**, 401–407 (2019). https://doi.org/10.1134/S1990793119030163
20. Liemburg-Apers, D.C., Imamura, H., Forkink, M., Nooteboom, M., Swarts, H.G., Brock, R., Smeitink J.A.M., Willems P.H.G.M., Koopman, W.J.H.: Quantitative glucose and ATP sensing in mammalian cells. Pharm. Res. **28**, 2745–2757 (2011). https://doi.org/10.1007/s11095-011-0492-8

21. Burilov, V.A., Fatikhova, G.A., Dokuchaeva, M.N., Nugmanov, R.I., Mironova, D.A., Dorovatovskii, P.V, Khrustalev V.N., Solovieva S.E., Antipin, I.S.: Synthesis of new p-tert -butylcalix[4]arene-based polyammonium triazolyl amphiphiles and their binding with nucleoside phosphates. Beilstein J. Org. Chem. **14**, 1980–1993 (2018). https://doi.org/10.3762/bjoc.14.173

22. Yamakawa, K., Nakano-Narusawa, Y., Hashimoto, N., Yokohira, M., Matsuda, Y.: Development and clinical trials of nucleic acid medicines for pancreatic cancer treatment. Int. J. Mol. Sci. **20**, 4224 (2019). https://doi.org/10.3390/ijms20174224

23. Ibragimova, R.R., Burilov, V.A., Aimetdinov, A.R., Mironova, D.A., Evtugyn, V.G., Osin, Y.N., Solovieva S.E., Antipin, I.S.: Polycationic derivatives of *p-tert*-butylthiacalix[4]arene in *1,3-alternate* stereoisomeric form: new DNA condensing agents. Macroheterocycles **9**, 433–441 (2016). https://doi.org/10.6060/mhc161180b

24. Kolb, H.C., Finn, M.G., Sharpless, K.B.: Click chemistry: diverse chemical function from a few good reactions. Angew. Chem. Int. Ed. **40**, 2004–2021 (2001). https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5

25. Thanigaiarasu, P.: Biomimetics in the design of medical devices. In Trends in development of medical devices (pp. 35–41). Elsevier (2020). https://doi.org/10.1016/B978-0-12-820960-8.00003-4

26. Schulze, B., & Schubert, U.S..: Beyond click chemistry – supramolecular interactions of 1,2,3-triazoles. Chem. Soc. Rev. **43**, 2522 (2014). https://doi.org/10.1039/c3cs60386e

27. Aziz Ali, A.: 1,2,3-Triazoles: synthesis and Biological Application. In Azoles - synthesis, properties, applications and perspectives. IntechOpen (2021). https://doi.org/10.5772/intechopen.92692

28. Guo, H.-Y., Chen, Z.-A., Shen, Q.-K., Quan, Z.-S.: Application of triazoles in the structural modification of natural products. J. Enzyme Inhib. Med. Chem. **36**, 1115–1144 (2021). https://doi.org/10.1080/14756366.2021.1890066

29. Malakhova, M., Gorbunov, A., Ozerov, N., Korniltsev, I., Ermolov, K., Bezzubov, S., Kovalev, V., Vatsouro, I.: Triazolated calix[4]semitubes: assembling strategies towards long multicalixarene architectures. Org. Chem. Front. **9**, 3084–3092 (2022). https://doi.org/10.1039/D2QO00432A

30. Gardiner, W.H., Camilleri, M., Martinez-Lozano, L.A., Bew, S.P., Stephenson, G.R.: Upper-rim monofunctionalisation in the synthesis of triazole- and disulfide-linked multicalix[4]- and -[6]arenes. Chem. Eur. J. **24**, 19089–19097 (2018). https://doi.org/10.1002/chem.201804755

31. Zhou, X., Pathak, P., Jayawickramarajah, J.: Design, synthesis, and applications of DNA–macrocyclic host conjugates. Chem. Commun. **54**, 11668–11680 (2018). https://doi.org/10.1039/C8CC06716C

32. Consoli, G.M.L., Granata, G., Geraci, C.: Design, synthesis, and drug solubilising properties of the first folate–calix[4]arene conjugate. Org. Biomol. Chem. **9**, 6491 (2011). https://doi.org/10.1039/c1ob06032e

33. Rusu, R., Szumna, A., Rosu, N., Dumea, C., Danac, R.: New triazole appended tert-butyl calix[4]arene conjugates: synthesis, Hg^{2+} binding studies. Tetrahedron **71**, 2922–2926 (2015). https://doi.org/10.1016/j.tet.2015.03.060

34. Požar, J., Cvetnić, M., Usenik, A., Cindro, N., Horvat, G., Leko, K., Modrusan, M., Tomišić, V.: The role of triazole and glucose moieties in alkali metal cation complexation by lower-rim tertiary-amide calix[4]arene derivatives. Molecules **27**, 470 (2022). https://doi.org/10.3390/molecules27020470

35. Kim, J.-S., Park, S.-Y., Kim, S.-H., Thuery, P., Souane, R., Matthews, S.E., Vicens, J.: A Pyrenyl-appended triazole-based calix[4]arene as a fluorescent sensor for iodide ion. Bull. Korean Chem. Soc. **31**, 624–629 (2010). https://doi.org/10.5012/bkcs.2010.31.03.624

36. Sonogashira, K., Tohda, Y., Hagihara, N.: A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. Tetrahedron Lett. **16**, 4467–4470 (1975). https://doi.org/10.1016/S0040-4039(00)91094-3

37. Armaroli, N., Accorsi, G., Rio, Y., Ceroni, P., Vicinelli, V., Welter, R., Gu, T., Saddik, M., Holler, M., Nierengarten, J.-F.: Electronic properties of oligophenylenevinylene and oligophenyleneethynylene arrays constructed on the upper rim of a calix[4]arene core. New J. Chem. **28**, 1627 (2004). https://doi.org/10.1039/b415063p

38. Dondoni, A., Marra, A. C-Glycoside clustering on calix[4]arene, adamantane, and benzene scaffolds through 1,2,3-triazole inkers. J. Org. Chem. **71**, 7546–7557 (2006). https://doi.org/10.1021/jo0607156

39. Desroches, C., Lopes, C., Kessler, V., Parola, S.: Design and synthesis of multifunctional thiacalixarenes and related metal derivatives for the preparation of sol–gel hybrid materials with non-linear optical properties. Dalton Trans. **10**, 2085–2092 (2003). https://doi.org/10.1039/B210252H

40. Yam, V. W.-W., Yip, S.-K., Yuan, L.-H., Cheung, K.-L., Zhu, N., Cheung, K.-K.: Synthesis, structure, and ion-binding properties of luminescent gold(I) alkynylcalix[4]crown-5 complexes. Organometallics **22**, 2630–2637 (2003). https://doi.org/10.1021/om030021c

41. He, X., Yam, V. W.-W.: A Highly selective bifunctional luminescence probe for potassium and fluoride Ions. Org. Lett. **13**, 2172–2175 (2011). https://doi.org/10.1021/ol200277n

42. Kašáková, M., Malinovská, L., Klejch, T., Hlaváčková, M., Dvořáková, H., Fujdiarová, E., Rottnerová, Z., Maťátková, O., Lhoták, P., Wimmerová, M., Moravcová, J.: Selectivity of original C-hexopyranosyl

calix[4]arene conjugates towards lectins of different origin. Carbohydr. Res. **469**, 60–72 (2018). https://doi.org/10.1016/j.carres.2018.08.012

43. Lim, C., Sandman, D.J., Sukwattanasinitt, M.: Topological polymerization of *tert*-butylcalix[4]arenes containing diynes. Macromolecules **41**, 675–681 (2008). https://doi.org/10.1021/ma0716128

44. Agrahari, A.K., Singh, A.K., Singh, A.S., Singh, M., Maji, P., Yadav, S., Rajkhowa, S., Prakash, P., Tiwari, V.K.: Click inspired synthesis of p-tert -butyl calix[4]arene tethered benzotriazolyl dendrimers and their evaluation as anti-bacterial and anti-biofilm agents. New J. Chem. **44**, 19300–19313 (2020). https://doi.org/10.1039/D0NJ02591G

45. Burilov, V.A., Valiyakhmetova, A.M., Aukhadieva, R.I., Solovieva, S.E., Antipin, I.S.: Synthesis of new p-tert-butylcalix[4]arene derivatives containing photopolymerizable 1,3-butadiyne fragments. Russ. J. Gen. Chem. **87**, 1946–1951 (2017). https://doi.org/10.1134/S1070363217090092

46. Matthews, S.E., Cecioni, S., O'Brien, J.E., MacDonald, C.J., Hughes, D.L., Jones, G.A., Ashworth, S.H., Vidal, S.: Fixing the conformation of calix[4]arenes: when are three carbons not enough? Chem. Eur. J. **24**, 4436–4444 (2018). https://doi.org/10.1002/chem.201705955

47. Muravev, A.A., Galieva, F.B., Strelnik, A.G., Nugmanov, R.I., Grüner, M., Solovieva, S.E., Latypov, S.K., Antipin, I.S., Konovalov, A.I.: Synthesis and structure of lower rim-substituted alkynyl derivatives of thiacalix[4]arene. Russ. J. Org. Chem. **51**, 1334–1342 (2015). https://doi.org/10.1134/S1070428015090213

48. Di Vincenzo, A., Palumbo Piccionello, A., Spinella, A., Chillura Martino, D., Russo, M., Lo Meo, P.: Polyaminoazide mixtures for the synthesis of pH-responsive calixarene nanosponges. Beilstein J. Org. Chem. **15**, 633–641 (2019). https://doi.org/10.3762/bjoc.15.59

49. Parola, S., Desroches, C.: Recent advances in the functionalizations of the upper rims of thiacalix[4]arenes. A review. Collect. Czechoslov. Chem. Commun. **69**, 966–983 (2004). https://doi.org/10.1135/cccc20040966

50. Zadmard, R., Junkers, M., Schrader, T., Grawe, T., Kraft, A.: Capsule-like assemblies in polar solvents. J. Org. Chem. **68**, 6511–6521 (2003). https://doi.org/10.1021/jo034592q

51. Burilov, V.A., Garipova, R.I., Solovieva, S.E., Antipin, I.S.: Synthesis of bifunctional derivatives of calix[4]arene bearing azidoalkyl fragments in cone stereoisomeric form. Dokl. Chem. **490**, 1–5 (2020). https://doi.org/10.1134/S0012500820010012

52. Burilov, V.A., Artemenko, A.A., Garipova, R.I., Amirova, R.R., Fatykhova, A.M., Borisova, J.A., Mironova, D.A., Sultanova, E.D., Evtugyn, V.G., Solovieva, S.E., Antipin, I.S.: New calix[4]arene-fluoresceine conjugate by click approach - synthesis and preparation of photocatalytically active solid lipid nanoparticles. Molecules **27**, 2436 (2022). https://doi.org/10.3390/molecules27082436

53. Fujii, S., Yamada, S., Araki, M., Lee, J. H., Takahashi, R., Sakurai, K.: Discrete and discontinuous increase in the micellar aggregation number: effects of the alkyl chain length on platonic micelles. Langmuir **35**, 3156–3161 (2019). https://doi.org/10.1021/acs.langmuir.8b04204

54. Fatykhova, G.A., Burilov, V.A., Dokuchaeva, M.N., Solov'eva, S.E., Antipin, I.S. Synthesis of tetraazide derivatives of *p-tert*-butylcalix[4]arene using copper-catalyzed nucleophilic aromatic substitution. Dokl. Chem. 479, 64-67 (2018). https://doi.org/10.1134/S0012500818040079

55. Maurin, A., Varatharajan, S., Colasson, B., Reinaud, O.: A water-soluble calix[4]arene-based ligand for the selective linear coordination and stabilization of copper(I) ion in aerobic conditions. Org. Lett. **16**, 5426–5429 (2014). https://doi.org/10.1021/ol502650c

56. Buttress, J.P., Day, D.P., Courtney, J.M., Lawrence, E.J., Hughes, D.L., Blagg, R.J., Crossley, A., Matthews, S.E., Redshaw, C., Bulman Page, P.C., Wildgoose, G.G.: "Janus" calixarenes: double-sided molecular linkers for facile, multianchor point, multifunctional, surface modification. Langmuir **32**, 7806–7813 (2016). https://doi.org/10.1021/acs.langmuir.6b02222

57. Zhang, T., Zhang, Z., Yue, Y., Hu,X., Huang, F., Shi, L., Liu, Y., Guo, D.: A general hypoxia-responsive molecular container for tumor-targeted therapy. Adv. Mater. **32**, 1908435 (2020). https://doi.org/10.1002/adma.201908435

58. Burilov, V., Makarov, E., Mironova, D., Sultanova, E., Bilyukova, I., Akyol, K., Evtugyn, V., Islamov, D., Usachev, K., Mukhametzyanov, T., Solovieva, S., Antipin, I.: Calix[4]arene polyamine triazoles: synthesis, aggregation and DNA binding. Int. J. Mol. Sci. **23**, 14889 (2022). https://doi.org/10.3390/ijms232314889

59. Jurisch, C.D., Arnott, G.E.: Attempted synthesis of a meta -metalated calix[4]arene. Beilstein J. Org. Chem. **15**, 1996–2002 (2019). https://doi.org/10.3762/bjoc.15.195

60. Luo, Z.-G., Zhao, Y., Xu, F., Ma, C., Xu, X.-M., Zhang, X.-M.: Synthesis and thermal properties of novel calix[4]arene derivatives containing 1,2,3-triazole moiety via K_2CO_3-catalyzed 1,3-dipolar cycloaddition reaction. Chin. Chem. Lett. **25**, 1346–1348 (2014). https://doi.org/10.1016/j.cclet.2014.05.013

61. Barboso, S., Carrera, A.G., Matthews, S.E., Arnaud-Neu, F., Böhmer, V., Dozol, J.-F., Rouquette, H., Schwing-Weill, M.-J.: Calix[4]arenes with CMPO functions at the narrow rim. Synthesis and extraction properties. J. Chem. Soc., Perkin Trans. 2 **4**, 719–724 (1999). https://doi.org/10.1039/a900210c

62. Ryu, E.-H., Zhao, Y.: Efficient Synthesis of water-soluble calixarenes using click chemistry. Org. Lett. **7**, 1035–1037 (2005). https://doi.org/10.1021/ol047468h

63. Gorbunov, A., Kuznetsova, J., Puchnin, K., Kovalev, V., Vatsouro, I.: Triazolated calix[4]arenes from 2-azidoethylated precursors: is there a difference in the way the triazoles are attached to narrow rims? New J. Chem. **43**, 4562–4580 (2019). https://doi.org/10.1039/C8NJ06464D

64. Gorbunov, A., Kuznetsova, J., Deltsov, I., Molokanova, A., Cheshkov, D., Bezzubov, S., Kovalev, V., Vatsouro, I.: Selective azide–alkyne cycloaddition reactions of azidoalkylated calixarenes. Org. Chem. Front. **7**, 2432–2441 (2020). https://doi.org/10.1039/D0QO00650E

65. Drigo, N.A., Gorbunov, A.N., Gorbunov, D.N., Talanova, M.Y., Kardasheva, Y.S., Kovalev, V.V., Maximov, A.L., Vatsouro, I.M.: Synthesis of polyfunctional phosphorus-containing calixarenes in cycloaddition reactions of azides to alkynes. Chem. Heterocycl. Compd. **52**, 1042–1053 (2016). https://doi.org/10.1007/s10593-017-2005-0

66. Burilov, V.A., Mironova, D.A., Ibragimova, R.R., Solovieva, S.E., König, B., Antipin, I.S. Thiacalix[4]arene-functionalized vesicles as phosphorescent indicators for pyridoxine detection in aqueous solution. RSC Adv. **5**, 101177–101185 (2015). https://doi.org/10.1039/C5RA18294H

67. Burilov, V., Valiyakhmetova, A., Mironova, D., Safiullin, R., Kadirov, M., Ivshin, K., Kataeva, O., Solovieva, S., Antipin, I.: "Clickable" thiacalix[4]arene derivatives bearing polymerizable 1,3-butadiyne fragments: synthesis and incorporation into polydiacetylene vesicles. RSC Adv. **6**, 44873–44877 (2016). https://doi.org/10.1039/C6RA07555J

68. Burilov, V.A., Mironova, D.A., Grygoriev, I.A., Valiyakhmetova, A.M., Solovieva, S.E., Antipin, I.S. Synthesis of water-soluble polyammonium thiacalix[4]arene derivative and its interaction with calf thymus DNA. Russ. J. Gen. Chem. **90**, 99–104 (2020). https://doi.org/10.1134/S1070363220010156

69. Hardman, M.J., Thomas, A.M., Carroll, L.T., Williams, L.C., Parkin, S., Fantini, J.L.: Synthesis and 'click' cycloaddition reactions of tetramethoxy- and tetrapropoxy-2-(ω-azidoalkyl)calix[4]arenes. Tetrahedron, **67**, 7027–7034 (2011). https://doi.org/10.1016/j.tet.2011.07.022

70. Fischer, C., Weber, E.: Bis-calix[4]arene-based podants using the bridge position as a constructive mode of subunit connection. J. Incl. Phenom. Macrocycl. Chem. **79**, 151–160 (2014). https://doi.org/10.1007/s10847-013-0338-6

71. Hertel, M.P., Behrle, A.C., Williams, S.A., Schmidt, J.A.R., Fantini, J.L.: Synthesis of amine, halide, and pyridinium terminated 2-alkyl-p-tert-butylcalix[4]arenes. Tetrahedron **65**, 8657–8667 (2009). https://doi.org/10.1016/j.tet.2009.08.033

72. Stejskal, F., Eigner, V., Dvorakova, H., Curinova, P., Lhotak, P.: Direct C–H azidation of calix[4]arene as a novel method to access meta substituted derivatives. Tetrahedron Lett. **56**, 5357–5361 (2015). https://doi.org/10.1016/j.tetlet.2015.08.002

73. Bew, S.P., Brimage, R.A., L'Hermit, N., Sharma, S.V.: Upper rim appended hybrid calixarenes via click chemistry. Org. Lett. **9**, 3713–3716 (2007). https://doi.org/10.1021/ol071047t

74. Galante, E., Geraci, C., Sciuto, S., Campo, V.L., Carvalho, I., Sesti-Costa, R., Guedes, P.M.M., Silva, J.S., Hill, L., Nepogodiev, S.A., Field, R.: A Glycoclusters presenting lactose on calix[4]arene cores display trypanocidal activity. Tetrahedron **67**, 5902–5912. (2011). https://doi.org/10.1016/j.tet.2011.06.065

75. Burilov, V.A., Nugmanov, R.I., Popova, E.V., Nabiullin, I.R., Solovieva, S.E., Antipin, I.S., Konovalov, A.I.: Bifunctional derivatives of (thia)calix[4]-arenes with terminal double and triple bonds: synthesis and azide-alkyne click reactions. Macroheterocycles **7**, 10–17 (2014). https://doi.org/10.6060/mhc140272b

76. Bicak, T.C., Gicevičius, M., Gokoglan, T.C., Yilmaz, G., Ramanavicius, A., Toppare, L., Yagci, Y.: Simultaneous and sequential synthesis of polyaniline-g-poly(ethylene glycol) by combination of oxidative polymerization and CuAAC click chemistry: a water-soluble instant response glucose biosensor material. Macromolecules **50**, 1824–1831 (2017). https://doi.org/10.1021/acs.macromol.7b00073

77. Spinella, A., Russo, M., Di Vincenzo, A., Chillura Martino, D., Lo Meo, P.: Hyper-reticulated calixarene polymers: a new example of entirely synthetic nanosponge materials. Beilstein J. Org. Chem. **14**, 1498–1507 (2018). https://doi.org/10.3762/bjoc.14.127

78. Yoon, H.Y., Lee, D., Lim, D., Koo, H., Kim, K.: Copper-free click chemistry: applications in drug delivery, cell Tracking, and tissue engineering. Adv. Mater. **34**, 10 (2022). https://doi.org/10.1002/adma.202107192

79. Rahman, S., Assiri, Y., Alodhayb, A.N., Beaulieu, L.Y., Oraby, A.K., Georghiou, P.E.: Naphthyl "capped" triazole-linked calix[4]arene hosts as fluorescent chemosensors towards Fe^{3+} and Hg^{2+}: an experimental and DFT computational study. New J. Chem. **40**, 434–440 (2016). https://doi.org/10.1039/C5NJ01362C

80. Georghiou, P.E., Rahman, S., Alrawashdeh, A., Alodhayb, A., Valluru, G., Unikela, K.S., Bodwell, G.J.: Synthesis, supramolecular complexation and DFT studies of a bis(pyrene)-appended 'capped' triazole-linked calix[4]arene as Zn^{2+} and Cd^{2+} fluorescent chemosensors. Supramol. Chem. **32**, 325–333 (2020). https://doi.org/10.1080/10610278.2020.1739686

81. Sultan, S., Shah, A., Khan, B., Nisar, J., Shah, M.R., Ashiq, M.N., Akhter, M.S., Shah, A.H.: Calix[4]arene derivative-modified glassy carbon electrode: a new sensing platform for rapid, simultaneous, and picomolar detection of Zn(II), Pb(II), As(III), and Hg(II). ACS Omega **4**, 16860–16866 (2019). https://doi.org/10.1021/acsomega.9b01869

82. Nag, R., Polepalli, S., Althaf Hussain, M., Rao, C.P.: Ratiometric Cu^{2+} binding, cell imaging, mitochondrial targeting, and anticancer activity with nanomolar IC_{50} by spiro-indoline-conjugated calix[4]arene. ACS Omega **4**, 13231–13240 (2019). https://doi.org/10.1021/acsomega.9b01402

83. Hosseinzadeh, R., Domehri, E., Tajbakhsh, M., Bekhradnia, A.: New fluorescent sensor based on a calix[4]arene bearing two triazole–coumarin units for copper ions: application for Cu^{2+} detection in human blood serum. J. Incl. Phenom. Macrocycl. Chem. **93**, 245–252 (2019). https://doi.org/10.1007/s10847-018-0872-3

84. Zhao, J.-L., Tomiyasu, H., Wu, C., Cong, H., Zeng, X., Rahman, S., Georghiou, P.E., Hughes, D. L., Redshaw, C., Yamato, T.: Synthesis, crystal structure and complexation behaviour study of an efficient Cu^{2+} ratiometric fluorescent chemosensor based on thiacalix[4]arene. Tetrahedron **71**, 8521–8527 (2015). https://doi.org/10.1016/j.tet.2015.09.038

85. Alodhayb, A.N., Braim, M., Beaulieu, L.Y., Valluru, G., Rahman, S., Oraby, A.K., Georghiou, P.E.: Metal ion binding properties of a bimodal triazolyl-functionalized calix[4]arene on a multi-array microcantilever system. Synthesis, fluorescence and DFT computation studies. RSC Adv. **6**, 4387–4396 (2016). https://doi.org/10.1039/C5RA12685A

86. Chen, Y.-J., Chen, M.-Y., Lee, K.-T., Shen, L.-C., Hung, H.-C., Niu, H.-C., Chung, W.-S.: 1,3-Alternate calix[4]arene functionalized with Pyrazole and triazole ligands as a highly selective fluorescent sensor for Hg^{2+} and Ag^{+} Ions. Front. Chem. **8**, *593261* (2020). https://doi.org/10.3389/fchem.2020.593261

87. Zhao, H., Zhan, J., Zou, Z., Miao, F., Chen, H., Zhang, L., Cao, X., Tian, D., Li, H.: Novel 1,3-alternate thiacalix[4]arenes: click synthesis, silver ion binding and self-assembly. RSC Adv. **3**, 1029–1032 (2013). https://doi.org/10.1039/C2RA22831A

88. Ovsyannikov, A.S., Epifanova, N.A., Popova, E.V., Kyritsakas, N., Ferlay, S., Hosseini, M.W., Latypov, S.K., Solovieva, S.E., Antipin, I.S., Konovalov, A.I.: Template synthesis of tetrakis-triazolylthiacalix[4]arene in the cone conformation and supramolecular structure of its hexanuclear complex with Ag(I). Macroheterocycles **7**, 189–195 (2014). https://doi.org/10.6060/mhc140273s

89. Donnelly, K.F., Lalrempuia, R., Müller-Bunz, H., Albrecht, M.: Regioselective electrophilic C–H bond activation in triazolylidene metal complexes containing a N-bound phenyl substituent. Organometallics **31**, 8414–8419 (2012). https://doi.org/10.1021/om300983m

90. Nehra, A., Yarramala, D.S., Rao, C.P.: A 1,3-capped calix[4]conjugate possessing an amine moiety as an anion receptor: reversible anion sensing detected by spectroscopy and characterization of the supramolecular features by microscopy. Chem. Eur. J. **22**, 8980–8989 (2016). https://doi.org/10.1002/chem.201600609

91. Hosseinzadeh, R., Maliji, F., Golchoubian, H., Bekhradnia, A.: A novel ferrocene-based calix[4]arene as an efficient optical and electrochemical sensor for highly selective fluoride recognition. ChemistrySelect, **4**, 3914–3920 (2019). https://doi.org/10.1002/slct.201900241

92. Feng, J., Yang, G., Mei, Y., Cao, X., Wang, Y., Li, H., Lu, Q.: Macroscopic visual detection of phoxim by calix[4]arene-based host-guest chemistry. Sens. Actuators B Chem. **271**, 264–270 (2018). https://doi.org/10.1016/j.snb.2018.05.107

93. Quan, J., Nie, G., Xue, H., Luo, L., Zhang, R., Li, H. Macroscopic chiral recognition by calix[4]arene-based host–guest interactions. Chem. Eur. J. **24**, 15502–15506 (2018). https://doi.org/10.1002/chem.201803564

94. Muravev, A.A., Agarkov, A.S., Galieva, F.B., Yakupov, A.T., Bazanova, O.B., Rizvanov, I.K., Shokurov, A.V., Zaitseva, A.V., Selektor, S.L., Solovieva, S. E., Antipin, I.S.: New terpyridine derivatives of thiacalix[4]arenes in solution and at the water-air interface. Russ. Chem. Bull. **69**, 339–350 (2020). https://doi.org/10.1007/s11172-020-2766-y

95. Nag, R., Vashishtha, M., Rao, C.P.: Switching the ion selectivity from Fe^{3+} to Al^{3+} by a triazole-appended calix[4]arene-based amphiphile. ChemistrySelect **3**, 1248–1256 (2018). https://doi.org/10.1002/slct.201702999

96. Chang, K.-C., Su, I.-H., Senthilvelan, A., Chung, W.-S.: Triazole-modified calix[4]crown as a novel fluorescent on-off switchable chemosensor. Org. Lett. **9**, 3363–3366 (2007). https://doi.org/10.1021/ol071337+

97. Zhan, J., Tian, D., Li, H.: Synthesis of calix[4]crowns containing soft and hard ion binding sites via click chemistry. New J. Chem. **33**, 725–728 (2009). https://doi.org/10.1039/B816467C

98. Morales-Sanfrutos, J., Ortega-Muñoz, M., Lopez-Jaramillo, J., Hernandez-Mateo, F., Santoyo-Gonzalez, F.: Synthesis of calixarene-based cavitands and nanotubes by click chemistry. J. Org. Chem. **73**, 7768–7771 (2008). https://doi.org/10.1021/jo801325c

99. Khan, B., Shah, M.R., Rabnawaz, M.: Synthesis of novel macrocycles carrying pincer-type ligands as future candidates for potential applications in size-selective, stereochemical and recyclable catalysts. J. Mol. Struct. **1155**, 734–744 (2018). https://doi.org/10.1016/j.molstruc.2017.11.040

100. Muravev, A.A., Laishevtsev, A.I., Galieva, F.B., Bazanova, O.B., Rizvanov, I.K., Korany, A., Solovieva, S.E., Antipin, I.S., Konovalov, A.I.: Azide–akyne click approach to the preparation of dendrimer–type multi(thia)calix[4]arenes with triazole linkers. Macroheterocycles **10**, 203–214 (2017). https://doi.org/10.6060/mhc170304m

101. Thulasi, S., Savithri, A., Varma, R.L.: Calix[4]bis(spirodienone) as a versatile synthon for upper rim alkoxylation of calixarenes and synthesis of novel triazole-based biscalixarene by 'CuAAC' chemistry. Supramol. Chem. **23**, 501–508 (2011). https://doi.org/10.1080/10610278.2011.556252

102. Läppchen, T., Dings, R.P.M., Rossin, R., Simon, J.F., Visser, T.J., Bakker, M., Walhe, P., van Mourik, T., Donato, K., van Beijnum, J.R., Griffioen, A.W., Lub, J., Robillard, M.S., Mayo, K.H., Grüll, H.: Novel analogs of antitumor agent calixarene 0118: synthesis, cytotoxicity, click labeling with 2-[18F]fluoroethylazide, and *in vivo* evaluation. Eur. J. Med. Chem. **89**, 279–295 (2015). https://doi.org/10.1016/j.ejmech.2014.10.048

103. Dings, R.P.M., Miller, M.C., Nesmelova, I., Astorgues-Xerri, L., Kumar, N., Serova, M., Chen, X., Raymond, E., Hoye, T.R., Mayo, K.H.: Antitumor agent Calixarene 0118 targets human galectin-1 as an allosteric inhibitor of carbohydrate binding. J. Med. Chem. **55**, 5121–5129 (2012). https://doi.org/10.1021/jm300014q

104. Malakhova, M., Gorbunov, A., Lentin, I., Kovalev, V., Vatsouro, I.: Switchable silver-ion complexation by triazolated calix[4]semitubes. Org. Biomol. Chem. **20**, 8092–8103 (2022). https://doi.org/10.1039/D2OB01588A

105. Feast, G.C., Lepitre, T., Mulet, X., Conn, C.E., Hutt, O.E., Savage, G.P., Drummond. C.J.: The search for new amphiphiles: synthesis of a modular, high-throughput library. Beilstein J. Org. Chem. **10**, 1578 (2014). https://doi.org/10.3762/bjoc.10.163

106. Hutt, O.E., Mulet, X., Savage, G.P.: Click-chemistry as a mix-and-match kit for amphiphile synthesis. ACS Comb. Sci. **14**, 565 (2012). https://doi.org/10.1021/co300080g

107. Gou, P.-F., Zhu, W.-P., Shen, Z.-Q.: Calixarene-centered amphiphilic A_2B_2 miktoarm star copolymers based on poly(ε-caprolactone) and poly(ethylene glycol): synthesis and self-assembly behaviors in water. J. Polym. Sci., Part A: Polym. Chem. **48**, 5643–5651 (2010). https://doi.org/10.1002/pola.24316

108. Fujii, S., Sanada, Y., Nishimura, T., Akiba, I., Sakurai, K., Yagi, N., Mylonas, E: A stimulus-responsive shape-persistent micelle bearing a calix[4]arene building block: reversible pH-dependent transition between spherical and cylindrical forms. Langmuir **28**, 3092–3101 (2012). https://doi.org/10.1021/la2037668

109. Fujii, S., Sakurai, K., Okobira, T., Ohta, N., Takahara, A.: Synthesis and characterization of a calix[4]arene amphiphilie bearing cysteine and uniform Au nanoparticle formation templated by its four cysteine moieties. Langmuir **29**, 13666–13675 (2013). https://doi.org/10.1021/la403377a

110. Fujii, S., Nishina, K., Yamada, S., Mochizuki, S., Ohta, N., Takahara, A., Sakurai, K.: Micelles consisting of choline phosphate-bearing calix[4]arene lipids. Soft Matter **10**, 8216–8223 (2014). https://doi.org/10.1039/C4SM01355G

111. Yoshida, K., Fujii, S., Takahashi, R., Matsumoto, S., Sakurai, K.: Self-assembly of calix[4]arene-based amphiphiles bearing polyethylene glycols: another example of "Platonic micelles." Langmuir **33**, 9122–9128 (2017). https://doi.org/10.1021/acs.langmuir.7b02196

112. Fujii, S., Takahashi, R., Sakurai, K.: Glutamic acids bearing calix[4]arene micelles: pH-controllable aggregation number corresponding to regular polyhedra. Langmuir **33**, 4019–4027 (2017). https://doi.org/10.1021/acs.langmuir.7b00603

113. Lee, J.H., Fujii, S., Takahashi, R., Sakurai, K.: Morphological transition of oppositely charged calix[4]arene surfactant mixture. Langmuir **34**, 12109–12115 (2018). https://doi.org/10.1021/acs.langmuir.8b02542

114. Mylonas, E., Yagi, N., Fujii, S., Ikesue, K., Ueda, T., Moriyama, H., Sanada, Y., Uezu, K., Sakurai, K., Okobira, T.: Structural analysis of a calix[4]arene-based Platonic Micelle. Sci. Rep. **9**, 1982 (2019). https://doi.org/10.1038/s41598-018-38280-1

115. Burilov, V., Valiyakhmetova, A., Mironova, D., Sultanova, E., Evtugyn, V., Osin, Y., Katsyuba, S., Burganov, T., Solovieva, S., Antipin, I.: Novel amphiphilic conjugates of *p-tert* -butylthiacalix[4]arene with 10,12-pentacosadiynoic acid in *1,3-alternate* stereoisomeric form. Synthesis and chromatic properties in the presence of metal ions. New J. Chem. **42**, 2942–2951 (2018). https://doi.org/10.1039/C7NJ04099G

116. Valiyakhmetova, A.M., Sultanova, E.D., Burilov, V.A., Solovieva, S.E., Antipin, I.S.: New DNA-sensor based on thiacalix[4]arene-modified polydiacetylene particles. Russ. Chem. Bull. **68**, 1067–1074 (2019). https://doi.org/10.1007/s11172-019-2521-4

117. Burilov, V., Fatykhova, A., Mironova, D., Sultanova, E., Nugmanov, R., Artemenko, A., Volodina, A., Daminova, A., Evtugyn, V., Solovieva, S., Antipin, I.: Oxyethylated fluoresceine-(thia)calix[4]arene conjugates: synthesis and visible-light photoredox catalysis in water–organic media. Molecules **28**, 261 (2022). https://doi.org/10.3390/molecules28010261

118. Sreedevi, P., Nair, J.B., Preethanuj, P., Jeeja, B.S., Suresh, C.H., Maiti, K.K., Varma, R.L.: Calix[4]arene based redox sensitive molecular probe for SERS guided Recognition of labile iron pool in tumor cells. Anal. Chem. **90**, 7148–7153 (2018). https://doi.org/10.1021/acs.analchem.8b01982

119. Ramachandran, M., Anandan, S., Ashokkumar, M.: A luminescent on–off probe based calix[4]arene linked through triazole with ruthenium(II) polypyridine complexes to sense copper(II) and sulfide ions. New J. Chem. **43**, 9832–9842 (2019). https://doi.org/10.1039/C9NJ01632E

120. Bono, N., Pennetta, C., Sganappa, A., Giupponi, E., Sansone, F., Volonterio, A., Candiani, G.: Design and synthesis of biologically active cationic amphiphiles built on the calix[4]arene scaffold. Int. J. Pharm. **549**, 436–445 (2018). https://doi.org/10.1016/j.ijpharm.2018.08.020

121. Mironova, D., Makarov, E., Bilyukova, I., Akyol, K., Sultanova, E., Evtugyn, V., Davletshin, D., Gilyazova, E., Bulatov, E., Burilov, V., Solovieva, S., Antipin, I. Aggregation, cytotoxicity and DNA binding in a series of calix[4]arene amphiphile containing aminotriazole groups. Pharmaceutics **16**, 699 (2023). https://doi.org/10.3390/ph16050699

122. Samanta, K., Ranade, D.S., Upadhyay, A., Kulkarni, P.P., Rao, C.P.: A bimodal, cationic, and water-soluble calix[4]arene conjugate: design, synthesis, characterization, and transfection of red fluorescent protein encoded plasmid in cancer cells. ACS Appl. Mater. Interfaces **9**, 5109–5117 (2017). https://doi.org/10.1021/acsami.6b14656

123. Altaf, A.A., Hashmat, U., Yousaf, M., Lal, B., Ullah, S., Holder, A.A., Badshah, A.: Synthesis and characterization of azo-guanidine based alcoholic media naked eye DNA sensor. R. Soc. Open Sci. **3**, 160351 (2016). https://doi.org/10.1098/rsos.160351

124. Costas-Lago, M.C., Vila, N., Rahman, A., Besada, P., Rozas, I., Brea, J., Loza, M.I., González-Romero, E., Terán, C.: Novel pyridazin-3(2H)-one-based guanidine derivatives as potential DNA minor groove binders with anticancer activity. ACS Med. Chem. Lett. **13**, 463–469 (2022). https://doi.org/10.1021/acsmedchemlett.1c00633

125. Staszewski, M., Nelic, D., Jończyk, J., Dubiel, M., Frank, A., Stark, H., Bajda, M., Jakubik, J., Walczyński, K.: Guanidine derivatives: how simple structural modification of Histamine H_3R antagonists has led to the discovery of potent muscarinic M_2R/M_4R antagonists. ACS Chem. Neurosci. **12**, 2503–2519 (2021). https://doi.org/10.1021/acschemneuro.1c00237

126. Gallego-Yerga, L., Lomazzi, M., Franceschi, V., Sansone, F., Ortiz Mellet, C., Donofrio, G., Casnati, A., García Fernández, J.M.: Cyclodextrin- and calixarene-based polycationic amphiphiles as gene delivery systems: a structure–activity relationship study. Org. Biomol. Chem. **13**, 1708–1723 (2015). https://doi.org/10.1039/C4OB02204A

127. Ahmed, F., Perveen, S., Shah, K., Shah, M.R., Ahmed, S.: Synthesis and characterization of triazole based supramolecule for interaction with cefuroxime in tap water and blood plasma. Ecotoxicol. Environ. Saf. **147**, 49–54 (2018). https://doi.org/10.1016/j.ecoenv.2017.08.023

128. Lo Meo, P., Lazzara, G., Liotta, L., Riela, S., Noto, R.: Cyclodextrin–calixarene co-polymers as a new class of nanosponges. Polym. Chem. **5**, 4499–4510 (2014). https://doi.org/10.1039/C4PY00325J

129. Cinà, V., Russo, M., Lazzara, G., Chillura Martino, D., Lo Meo, P.: Pre- and post-modification of mixed cyclodextrin-calixarene co-polymers: a route towards tunability. Carbohydr. Polym **157**, 1393–1403 (2017). https://doi.org/10.1016/j.carbpol.2016.11.018

130. Di Vincenzo, A., Russo, M., Cataldo, S., Milea, D., Pettignano, A., Lo Meo, P.: Effect of pH variations on the properties of cyclodextrin-calixarene nanosponges. ChemistrySelect **4**, 6155–6161 (2019). https://doi.org/10.1002/slct.201901200

131. Fontana, R. M., Milano, N., Barbara, L., Di Vincenzo, A., Gallo, G., Lo Meo, P.: Cyclodextrin-calixarene nanosponges as potential platforms for pH-dependent delivery of tetracycline. ChemistrySelect **4**, 9743–9747 (2019). https://doi.org/10.1002/slct.201902373

132. Moni, L., Pourceau, G., Zhang, J., Meyer, A., Vidal, S., Souteyrand, E., Dondoni, A., Morvan, F., Chevolot, Y., Vasseur, J.-J., Marra, A.: Design of triazole-tethered glycoclusters exhibiting three different spatial arrangements and comparative study of their affinities towards PA-IL and RCA 120 by using a DNA-based glycoarray. ChemBioChem **10**, 1369–1378 (2009). https://doi.org/10.1002/cbic.200900024

133. Konvalinkova, D., Dolnicek, F., Hovorkova, M., Cerveny, J., Kundrat, O., Pelantova, H., Petraskova, L., Cvacka, J., Faizulina, M., Varghese, B., Kovaricek, P., Kren, V., Lhotak, P., Bojarová, P.: Glycocalix[4]arenes and their affinity to a library of galectins: the linker matters. Org. Biomol. Chem. **21**, 1294–1302 (2023). https://doi.org/10.1039/D2OB02235D

134. Burilov, V., Mironova, D.A., Ibragimova, R.R., Solovieva, S.E., Antipin, I.S.: Interactions of new bis-ammonium thiacalix[4]arene derivatives in *1,3-alternate* stereoisomeric form with bovine serum albumin. BioNanoScience **6**, 427–430. (2016). https://doi.org/10.1007/s12668-016-0255-4

135. Burilov, V.A., Mironova, D.A., Ibragimova, R.R., Nugmanov, R.I., Solovieva, S.E., Antipin, I.S.: Detection of sulfate surface-active substances via fluorescent response using new amphiphilic thiacalix[4]arenes bearing cationic headgroups with Eosin Y dye. Colloids Surf. A: Physicochem. Eng. Asp. **515**, 41–49 (2017). https://doi.org/10.1016/j.colsurfa.2016.12.007