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SHORT REVIEW

Calix[4]API-s: fully functionalized calix[4]arene-based facial active pharmaceutical ingredients

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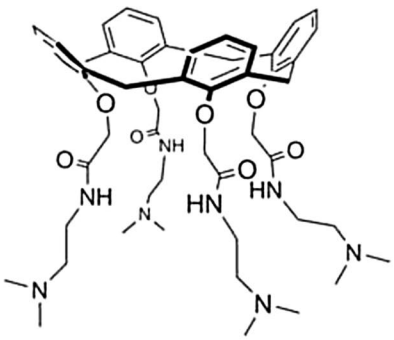
Abstract

This mini-review covers 25 fully functionalized facial calix[4]arene-based symmetrical and conical cyclic tetramers with significant (comparable to established therapeutic agents) anticancer and anti-infective activities. The main role of the calixarene scaffold in these calix[4]arene-based active pharmaceutical ingredients (calix[4]API-s) is to replicate embedded phenolic units in the cyclic tetramers. So, probably owing to the multivalency, facial, conical structures of calix[4]API-s and synergistic effect of their four replicated units, they can be considered as effective bioactive agents.

Graphic abstract



OTX008: The most successful **Calixapi** to date
The fully functionalized calix[4]arene-based facial active pharmaceutical ingredient
in the the field of anticancer agents.

Keywords Calix[4]arene · Active pharmaceutical ingredient · Anticancer · Anti-infective · Cyclic tetramer

Introduction

The term calixarene is derived from the Greek *calix* meaning "chalice" and was first used by Gutsche in 1978 to describe a new class of macrocycles consisting of repeating phenolic units with methylene bridges (cyclic oligomers of phenols) [1]. To date, these structures have found various biological applications (Fig. 1) [2]. In addition, they have no apparent cytotoxicity and immunogenicity, especially in water soluble derivatives [3, 4]. The strength in the synthesis of calixarenes is the lack of pollutants in the products [4]. It means that none of the toxic reagents (phenol and formaldehyde) used in their synthesis are found in the products.

Special features of calix[4]arenes: the limited systemic toxicity (no immune response), ease of functionalization or modification, ease of shaping in four different three-dimensional conformations (flexibility), and rigidity make them superior scaffolds for the designing and development

To my lovely children, Helena & Elvin.

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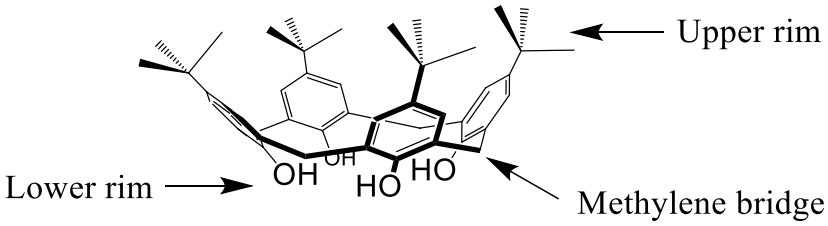


Fig. 1 Chaliced-shape of *p–t*-butyl-Calix[4]arene

of novel bioactive agents [2]. The fully functionalized cone calix[4]arenes, having a "facial" and constrained disposition of repeating units, are more suitable for interaction with large surfaces of target sites on biomolecules. In facial structures, functional groups (active moieties) are located only on one side of the structure, and in the case of calix[4]arenes, this side can be one of the lower or the upper rims [4].

Since the active pharmaceutical ingredient (API) refers to the drug active ingredient, the main scope of this short-review as the first exhaustive overview is to cover and investigate calix[4]arene-based API-s (calix[4]API-s) with comparable bioactivities to standard drug samples. All of the calix[4]API-s discussed in the present review have fully functionalized (with same units in a cluster form) structures with facial, conical, and symmetrical features. So, this review does not cover any other members of calixarenes family such as: oxa-, thia-, and aza-calix[4]arenes or any derivatives of calix[$n > 4$]arene and any partially functionalized or asymmetric bioactive calix[4]arenes. On the other hand, since bioactive structures with mediation (gene vectors and drug delivery) and prevention (antiradicals and antioxidants) features are not considered API-s, therefore, there is no discussion of them, here. So, the author herein just focused on 25 bioactive calix[4]API-s with remarkable and comparative biological activities with regard to reference API-s. Based on the fact that these structures consist of four repetitions, it can be supposed that their promising bioactivities, probably thanks to their facial, conical, the multivalency, synergistic effect of four impacted units and appropriate interaction with the target sites [2]. Study of these structures will become even more evident the importance of the calixarene applications in medicinal chemistry for achieving new APIs and will smooth a promising approach for the synthesis of similar bioactive compounds.

Owing to the diversity of bioactivity types of these calix[4]arene-based API-s, the review has been divided to two main sections: calix[4]API-based anticancer agents and calix[4]API-based anti-infective agents. The last section can be divided to more subsections such as calix[4]API-based antiviral, antibacterial, antifungal, and antiparasite agents.

Calix[4]API-based anticancer agents

Due to the same metabolic requirement of cancerous and healthy cells (this isn't in violation of the premise that tumor cells grow faster than normal cells), finding the optimal therapeutic anticancer agent for the disease treatment without any apparent toxicity for the patient (the minimum side effects) is the serious problem in cancer chemotherapy. This problem is known as non-selectivity in cancer treatment [5]. Therefore, the main reason for using new class of APIs such as functionalized calixarenes in the field of anticancer agents is to provide high toxicity toward cancerous cells with low toxicity to normal cells; this leads to appropriate selectivity and targeted chemotherapy.

The lectins, carbohydrate binding proteins, are very important bio-structures, because they are involved in many biological processes. A group of lectins that are responsible for recognizing galactosides on cell surfaces and involved in the progression and migration of tumors and metastases are called galectins. Glycosylated compounds can inhibit the activity of lectins. Based on this background, Mayo and his colleagues reported an inhibitor for human galectin-1 [6]. To date, it is the most successful calix[4]API in the field of anticancer agents (namely 0118 or OTX008, Fig. 2). This molecule endowed with tetra amine groups at the lower rim of calix[4]arene scaffold, as a topomimetic of anginex (a designer antiangiogenic peptide), that has managed by another research group [7] to gain entry to Phase I study

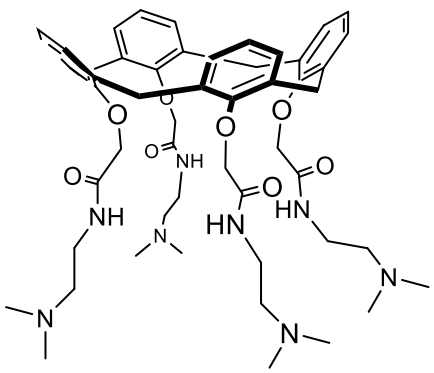


Fig. 2 Calix[4]API-based inhibitor of human galectin-1

in clinical trials as a noncompetitive allosteric inhibitor of human galectin-1 with potential cytostatic antitumor activity. The human galectin-1 is a protein that regulates cell proliferation and involved in carcinogenesis and migration of endothelial cells. Therefore, OTX008 as a galectin-1 inhibitor should be able to inhibit cell cycle progression, cell and tumor invasion, cell proliferation, tumor angiogenesis, and tumor growth. Also, due to the structural features of OTX008, as a non-peptidic and non-hydrolysable structure with chemical stability, it should have better in vivo exposure over anginex with peptidic and hydrolysable structure [8]. In fact, based on the results of in vivo and in vitro experiments by using OTX008, it acts as a multifunctional antitumor agent, i.e., a multiplier of the anti-proliferative effects of Semaphorin-3A in human head and neck cell line SQ20B ($GI_{50}=3$ μM) and a reverser of invasion induced by exogenous galectin-1 [7], a growth inhibitor of human ovarian cancer xenografts A2780-1A9 in mice (5 mg/kg, 20% better than anginex) [7], a endothelial cell proliferation inhibitor in a dose-dependent manner ($IC_{50}=2$ μM) [6], a tumor angiogenesis and tumor growth inhibitor in murine tumor models (i.e., MA148 human ovarian carcinoma and B16F10 murine melanoma) [6], a promotor of leukocyte infiltration into tumors [9], and a new potential target-therapy agent for the leukemia cells [10]. Due to the lack of any observable toxicity, as assessed by behavior, body weight change, or hematocrit or creatinine levels in treatment of animals by OTX008, it can be considered as a novel anticancer agent with the minimal side effects [6].

In 2013, Mayo's group in another study [11], via chemical modification of hydrophilic face (lower rim) of OTX008 discovered another novel fully functionalized calix[4]arene (namely PTX013, Fig. 3) which was more potent as a cytotoxic anti-tumor agent. PTX013 is particularly effective at inhibiting the growth of drug resistant cancer cells (i.e., in SQ20B via inducing cell cycle arrest and a reduction in DNA synthesis). In the syngeneic B16F10 model, PTX013 inhibits tumor growth in a dose-dependent manner with about 20-fold more efficient than parent OTX008. This significant difference among the functions of these antitumor agents indicated that, the reducing in the length of the hydrophilic face at the calix[4]arene structure by removing the amide groups at the lower rim and increasing the polarity of the compound, can significantly be improve bioactivity of structure. Moreover, due to the different types of cell proliferation inhibitory profiles of PTX013 and OTX008, PTX013 does not act as a human galectin-1 inhibitor and again, unlike OTX008 as a cytostatic agent, it is a cytotoxic anticancer agent.

In 2016 [12], a new calix[4]arene-based polyhydroxyamine (Fig. 4), bearing four O-acetyl ethanolamine groups at the lower rim, with cytotoxic effects at inhibiting the growth of six cancer cell lines, i.e., A549, SKOV3, SW1990, Hela, Raji, and MDA-MB-231 has been reported with good results based on IC_{50} values (3.7, 5.1, 3.3, 7.1, 4.7, and 3.4 μM, respectively). Moreover, the tert-butyl groups at the upper rim of calix[4]arene platform have significantly effect on its cytotoxic function.

In 2013, a new calixsugar (Fig. 5), carbohydrate-based functionalized calix[4]arene, endowed with the four hydrolytically stable mimetic of the tumor antigen GM3 lactone at the upper rim has been reported as a novel calix[4]API in the field of antitumor agents [13]. This structure was effective on A375 melanoma cells at reducing about twofold of cells capacity to adhere to endothelial cells, reducing about 2/3 metastatic potential of cells, and inducing 1/3 of cells apoptosis.

p53TD-R337H protein is a replication factor of tumor inhibitor that is mutated in about half of human cancers, and its function strongly depends on its tetrameric entirety. So, destabilization of the tetrameric structure could lead to a tissue disposed to cancerous [14]. In 2008, de Mendoza and his colleagues reported a calix[4]arene decorated by four cationic guanidiniomethyl groups at the upper rim and hydrophobic biscrown loops at the lower rim to stabilize the structure in a conformationally rigid and fixed conical shape (Fig. 6) [15]. This structure as a suitable cationic tetrameric ligand interacts appropriately with anionic residues of

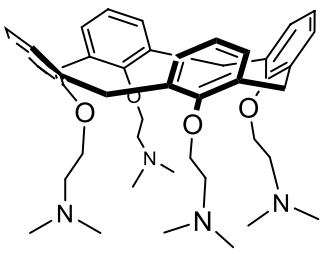


Fig. 3 Calix[4]API-based antitumor agent

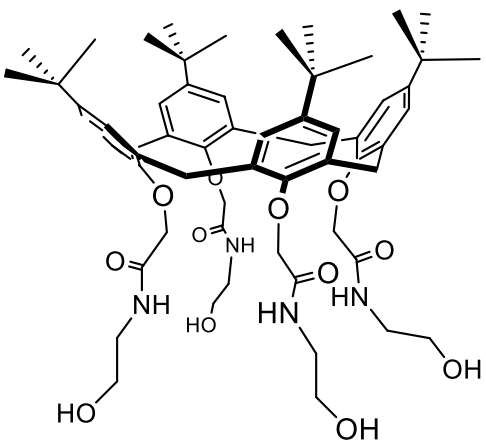
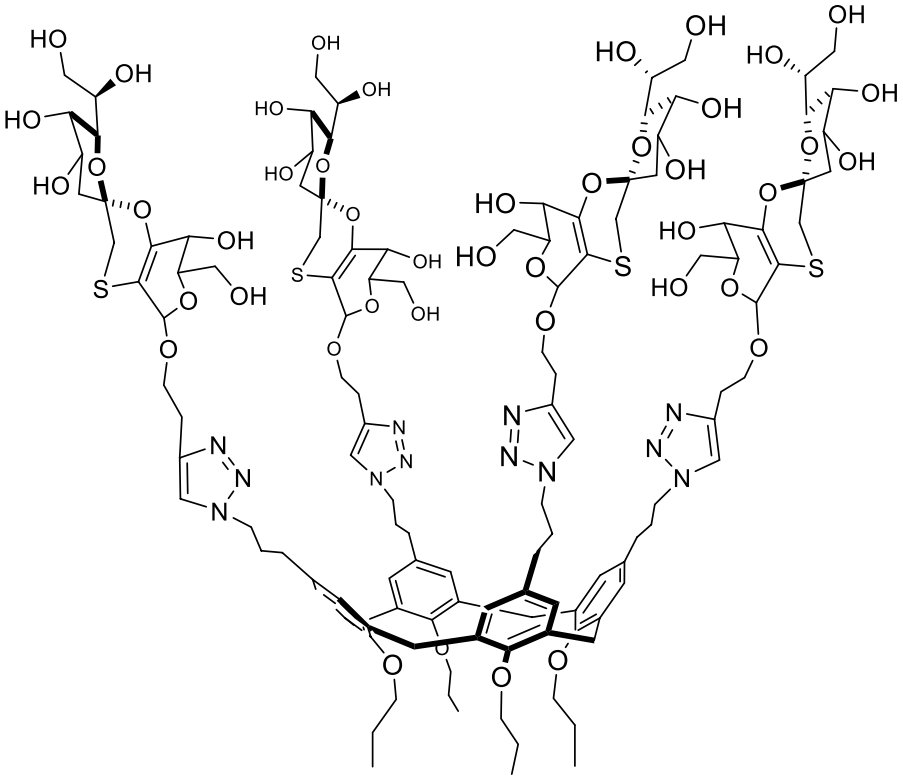


Fig. 4 Calix[4]API-based cytotoxic anticancer agent

Fig. 5 Calix[4]API-based calixsugar with antitumor activity



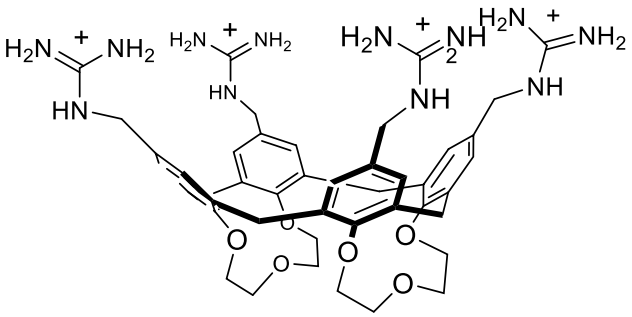


Fig. 6 Conformationally rigid Calix[4]API-based anticancer agent

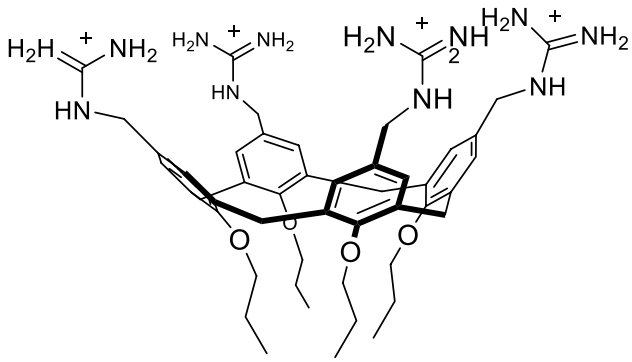


Fig. 7 Conformationally flexible Calix[4]API-based anticancer agent

the four domains of the mutated p53TD-R337H protein to complement the tetrameric shape of the protein and, consequently, prevents cells from turning cancerous.

In addition, this group in 2011, in another study reported a new conformationally flexible tetraguanidinium-calix[4]arene (Fig. 7) with improved potency in interaction with higher affinity to the mutated protein p53TD-R337H domains over its conformationally rigid analog [16]. Structural differentiation of these ligands is in their flexibilities. In detail, compared to previously reported analog, in the new structure by reducing the conical rigidity via replacing the biscrown loops at the lower rim with the four conformationally free propyl chains, the flexibility and, consequently, affinity of the tetrameric ligand to the target protein surface have been increased.

Since protein–protein interactions (PPI-s) are the origin of many biological phenomena in the body, therefore, controlling these interactions in medicinal chemistry is very important. This can be done by designing specific molecules with polar moieties that prevent PPIs. Following this type of approach, Hamilton and coworkers proposed a series of calix[4]arene ligands able to disrupt PPIs as anticancer agents.

Hamilton's team in 2000 [17] reported a calix[4]arene-based growth factor binder (namely GFB-111, Fig. 8), which was able to bind to platelet-derived growth factor (PDGF) as a novel protein surface binding agent and blocks binding of PDGF to its natural receptor (PDGFR). In detail, GFB-111

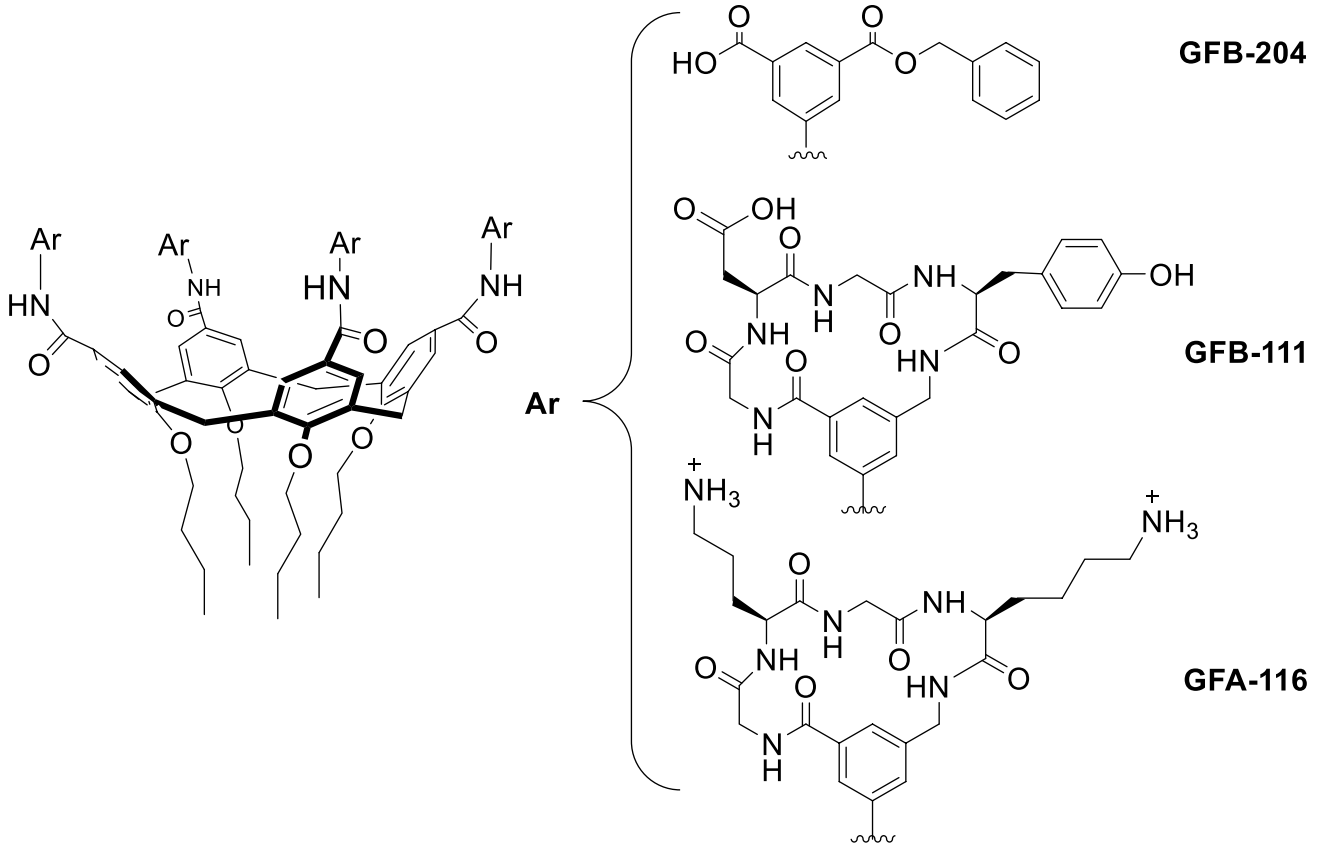


Fig. 8 Calix[4]API-based antibodies

inhibits auto-phosphorylation of PDGFR with high selectivity ($IC_{50}=0.25$ μM). Going over the structure of inhibitor, the calix[4]arene scaffold is decorated by four cyclic hexapeptide with negative and hydrophobic residues at the upper rim to bind positively charged and hydrophobic sites of PDGF. Owing to the ability of PDGF to stimulate angiogenesis and contribute to cancer cell growth, its synthetic binder GFB-111 should be able to inhibit tumor growth and angiogenesis. Therefore, in vivo experiments results, i.e., in the human glioblastoma U87MG and the human lung adenocarcinoma A-549 by using GFB-111 in the nude mouse human xenograft model, were confirmed the aforementioned hypothesis.

This group in 2004 reported another cyclohexapeptidomimetic calix[4]arene as a novel growth factor antagonist (namely GFA-116, Fig. 8), which was able to disrupt ($IC_{50}=0.5$ μM) binding of vascular endothelial growth factor (VEGF) to its natural receptor in a dose-dependent manner [18]. The structure of calix[4]arne-based inhibitor contains four cyclic hexapeptide at the upper rim of scaffold with strongly positively charged surface area to bind negative residues of VEGF. GFA-116 was able to inhibit tumor growth, metastasis, and angiogenesis of A-549 human lung tumors and B16-F10 melanoma cells in mice.

Owing to the fact that the necessity of VEGF in initiation and PDGF in the maintenance of angiogenesis, designing a synthetic dual inhibitor for the both target proteins would be desirable. So, Hamilton and his colleagues in 2005 reported a novel calix[4]arene-based growth factor binder (GFB-204, Fig. 8) which inhibits highly selective both PDGF and VEGF binding to their corresponding natural receptors ($IC_{50}=0.2$, 0.5 μM, respectively) and, consequently, blocks angiogenesis [19]. The structure of inhibitor, in place of the peptide loops, simply consists of acyclic isophthalic acid groups functionalized with carboxylic acid and hydrophobic benzylester at the upper rim of the calix[4]arene scaffold. GFB-204 had no effect on total body weight or organ weight and histopathology factors. GFB-204 also potently blocked the ability of endothelial cells to migrate ($IC_{50}=0.6$ μM) as well as its ability to inhibit properly growth of A-549 xenograft tumor in mice.

Calix[4]API-based anti-infective agents

Calix[4]API-s in this section can be divided to four subsections. Therefore, the author has divided this category to antiviral, antibacterial, antifungal, and anti-parasite agents for a good study.

Calix[4]API-based antiviral agents

Hamilton et al. [20] in 2010 reported a novel calix[4]arene-based dual antiviral agent (Fig. 9) as a proteomimetic compound with an interesting activity for blocking both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections. Maintaining the cone conformation (critical factor for antiviral activity) via tetrabutoxy groups at the lower rim and aromatic isophthalic spacers (essential for anti-HIV activity) bearing di-acid groups (necessary for the anti-HCV efficacy) at the upper rim of the calix[4]arene scaffold play key roles for function of compound as dual inhibitor agent. This confirms the dependence of antiviral activity on the shape and structure of the calix[4]arene. In vitro tests, this calix[4]API showed significant IC_{50} values for HIV (0.36 µM) and HCV (1.8 µM) with low cytotoxicity (> 50 µM). After 2 years, Hamilton et al. [21] showed the pathway of anti-HIV function of this inhibitor. Mechanistically, it is able to block HIV entry into cells by binding to the exterior surface of GP120, a protein on the viral envelope that binds to CD4 receptor on the cell surface and, consequently, results in the inhibition of HIV replication. Therefore, this compound is known as a novel GP120/CD4, protein–protein interaction, inhibitor in a dose-dependent manner.

Dondoni et al. [22] in 2008 reported two novel calix[4]arene-based clusters of sialic acids as conical antiviral agents (Fig. 10) which were able to inhibit the influenza A virus-induced hemagglutination with averagely 65 times more potencies over that of a single sialic acid unit.

Calix[4]API-based antibacterial agents

Regnouf-de-Vains and his coworkers in 2006 [23] showed that tetra-*para*-guanidino-ethyl-calix[4]arene (namely CX1, Fig. 11) with organized positive charges displays a significant antibacterial activity (MIC < 1 mg/L) against some strains of *Staphylococcus* and with particularly good efficiency (MICs = 2 mg/L) against clinical isolates for all *Escherichia coli* strains [24]. The four guanidinium groups

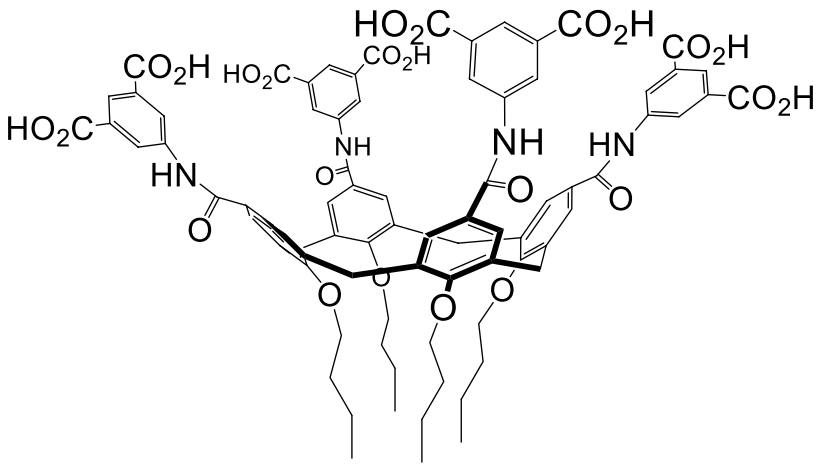


Fig. 9 Calix[4]API-based dual inhibitor for HIV and HCV

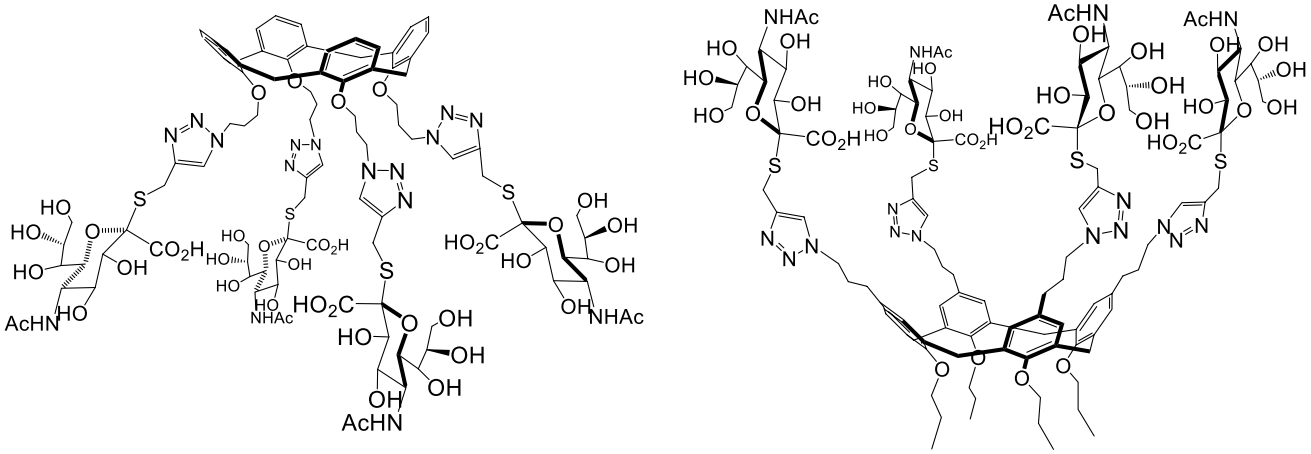


Fig. 10 Calix[4]API-based anti-influenza A agents

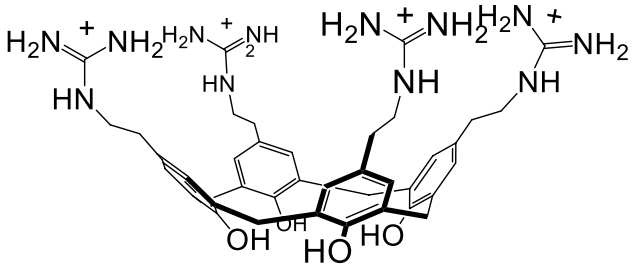


Fig. 11 Calix[4]API-based anti(myco)bacterial agent

interact with the negative charges of some specific components of the bacterial cell wall [24]. Organization four guanidinium groups at the upper rim could result in a synergistic effect in ionic interactions with membrane targets [24]. The effects of CX1 were disruption of the bacterial membrane, modification of electrophoretic mobility, and increased membrane permeability in different bacterial strains [25]. In another study [26], this compound was tested on the *Mycobacterium tuberculosis*, H_{37}Rv strain and it was as active (MIC = 0.8 mg/L, IC_{50} = 0.25 mg/L) as streptomycin with the value of MIC = 0.7 mg/L as a standard drug for clinical usage. Also, it was active against mutated strain of *M. tuberculosis* MYC5165 with values of MIC = 0.8 mg/L and IC_{50} = 0.1 mg/L. In the other words, CX1 showed minimum inhibitory concentration (MIC) values at same low level of 0.8 μM for both H37Rv reference and INH-resistant MYC5165 *M. tuberculosis* strains (16-fold more active than INH, a standard dug, against MYC5165 strain).

Nasuhi Pur et al. [27] reported two novel penicillin-calixarene hybrids (calixpenams, Fig. 12) with good bioactivities (~ 6-fold more efficient than their constitutive monomers, phenolic penicillins V and X) against three strains of *Streptococcus* (MIC = 0.002–0.125 μM).

This team in another study [28] introduced two novel cephalosporin-calixarene hybrids (calixcephems, Fig. 13) with good efficiency (tenfold more active than their corresponding monomers), specially against two methicillin-resistant strains of *Staphylococcus aureus* (MRSA) (MIC = 0.22–1.63 μM). In fact, these calix[4]API-s are analogous to the aforementioned calixpenams and synthetized by "the Morin ring expansion" of the penicillin

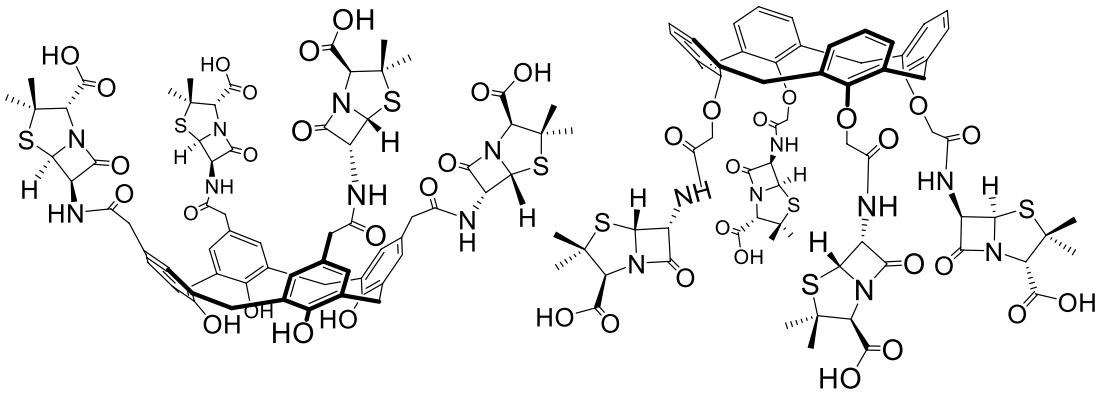


Fig. 12 Calix[4]API-based antibacterial agents

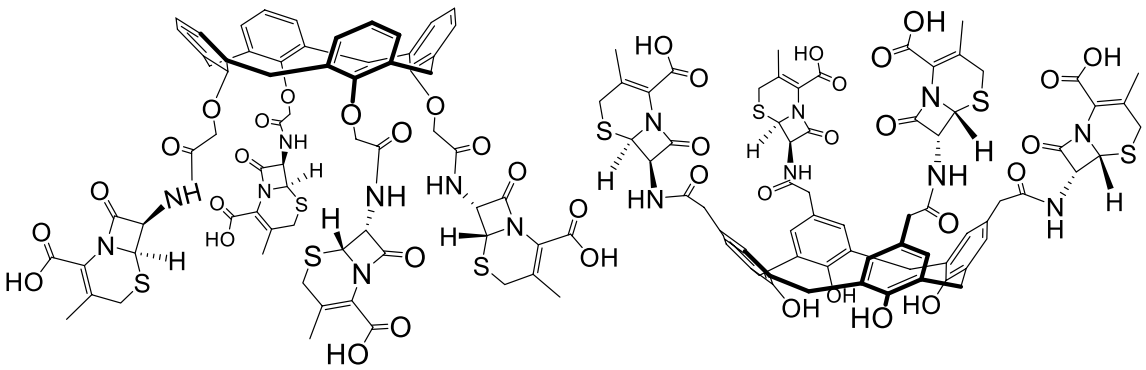


Fig. 13 Calix[4]API-based antibacterial agents

nuclei of the calixpenams to the constitutive cephem nuclei via sulfoxide intermediates.

Until recently, Consoli et al. [29] reported a new hydrophobic and polycationic calix[4]arene-based facial cavity, bearing *N*-methyldiethanol ammonium moieties at the upper rim and in a fixed cone conformation (Fig. 14), with interestingly significant antibacterial activity (MIC = 4 µg/ml) against methicillin-resistant Gram-positive *Staphylococcus* strains. Mechanistically, this calix[4]API can able to interact electrostatically with anionic parts of bacterial surface via its polycationic arms and hydrogen bonded to it via the OH groups. It is more effective (about 130-fold) than ofloxacin (positive control) against the resistant strains: methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE).

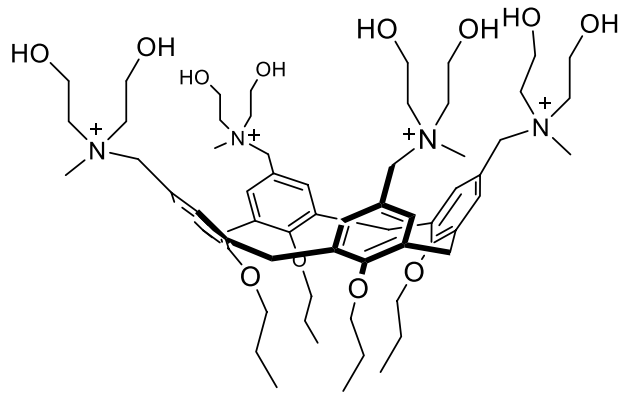


Fig. 14 Calix[4]API-based anti-MRSA and anti-MRSE agent

Calix[4]API-based antifungal agents

In a new study in 2006 [30], a novel symmetrical calix[4]arene-based cluster of amphotericin B (Fig. 15) with high antifungal activity against *Saccharomyces cereVisiae* BY4741 (MIC = 0.1 µM) and lower hemotoxicity (12-fold) with regards to that of monomeric amphotericin B has been reported.

In 2017, a new fully functionalized facial calix[4]arene bearing four pyrrolidine moieties at the upper rim of the scaffold has been reported (Fig. 16) with significant antifungal activities against *Aspergillus niger* (ATCC 16404) and *Aspergillus flavus* (ATCC 90906) with the values of MIC = 0.58 and 1.17 mg/L, respectively [31].

Calix[4]API-based anti-parasite agents

In 2016, a new fully functionalized calix[4]arene, bearing four 2-amino pyrimidine groups at the lower rim of the scaffold (Fig. 17) with anti-parasite activity against *plasmodium*

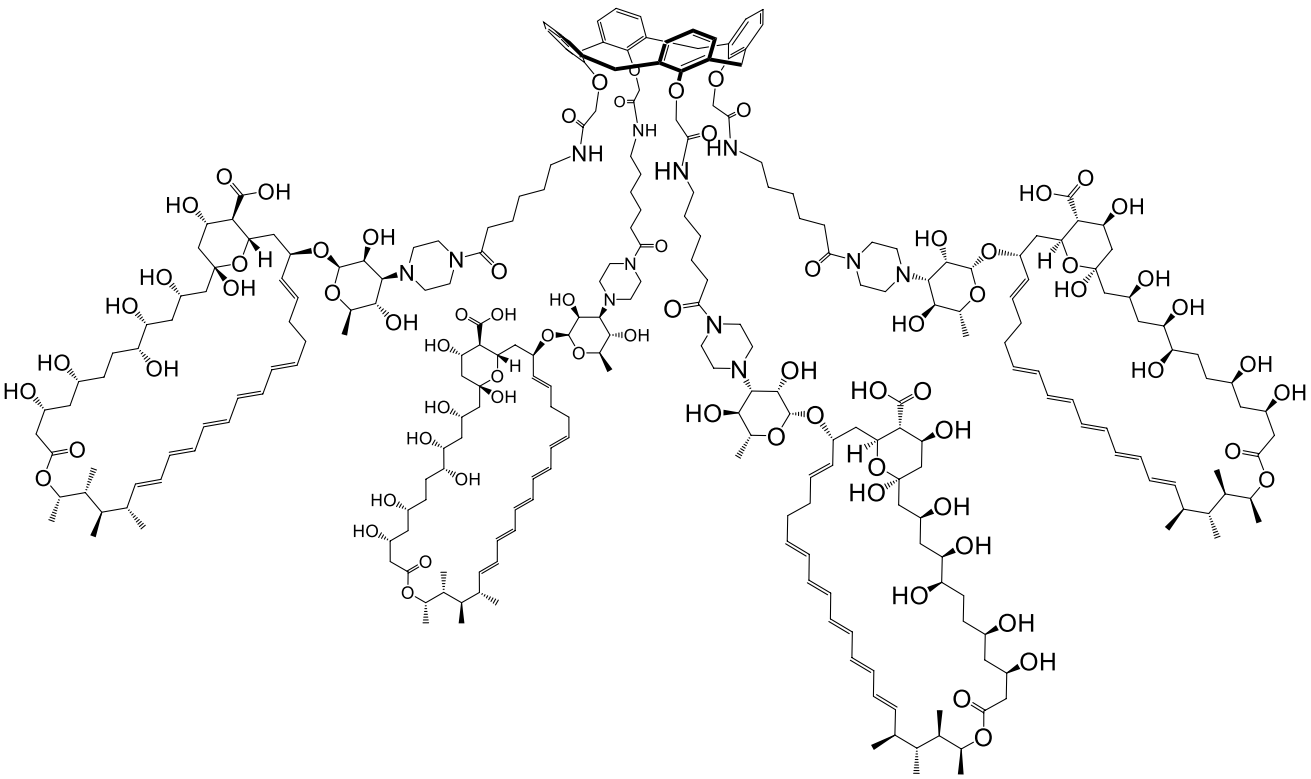


Fig. 15 Calix[4]API-based antifungal agent

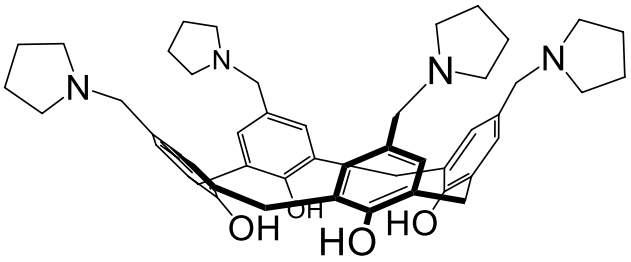


Fig. 16 Calix[4]API-based antifungal agent

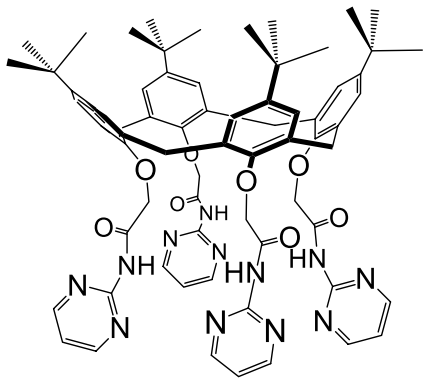


Fig. 17 Calix[4]API-based antimalarial agent

falciparum strains (IC_{50} = 0.043 mg/L, comparative to chloroquine with IC_{50} = 0.02 mg/L as the standard drug) has been reported as a novel antimalarial agent [32]. This compound inhibits hemozoin (β-hematin) formation by the malarial parasites. On the other hand, nitrogen atoms of pyrimidine rings and 2-amino groups increase the electronegativity, and consequently, enhancing the bio-function of molecule as an antimalarial agent.

In 2011, a new calixsugar with tetra triazole-modified β-lactosyl residues via spacers at the lower rim of calix[4] arene scaffold in cone conformation has been reported (Fig. 18) as a novel anti-parasite agent with in vitro trypanocidal activity against parasite *Trypanosoma cruzi* Y strain (IC_{50} = 68 μM) that was equipotent to benznidazole (IC_{50} = 67 μM) as the established anti-trypanosomal drug [33]. The length of linker between the calix[4]arene core and the β-lactosyl residues is an essential factor of compound for anti-*T. cruzi* activity.

Calix[4]API-based antiseptic agents

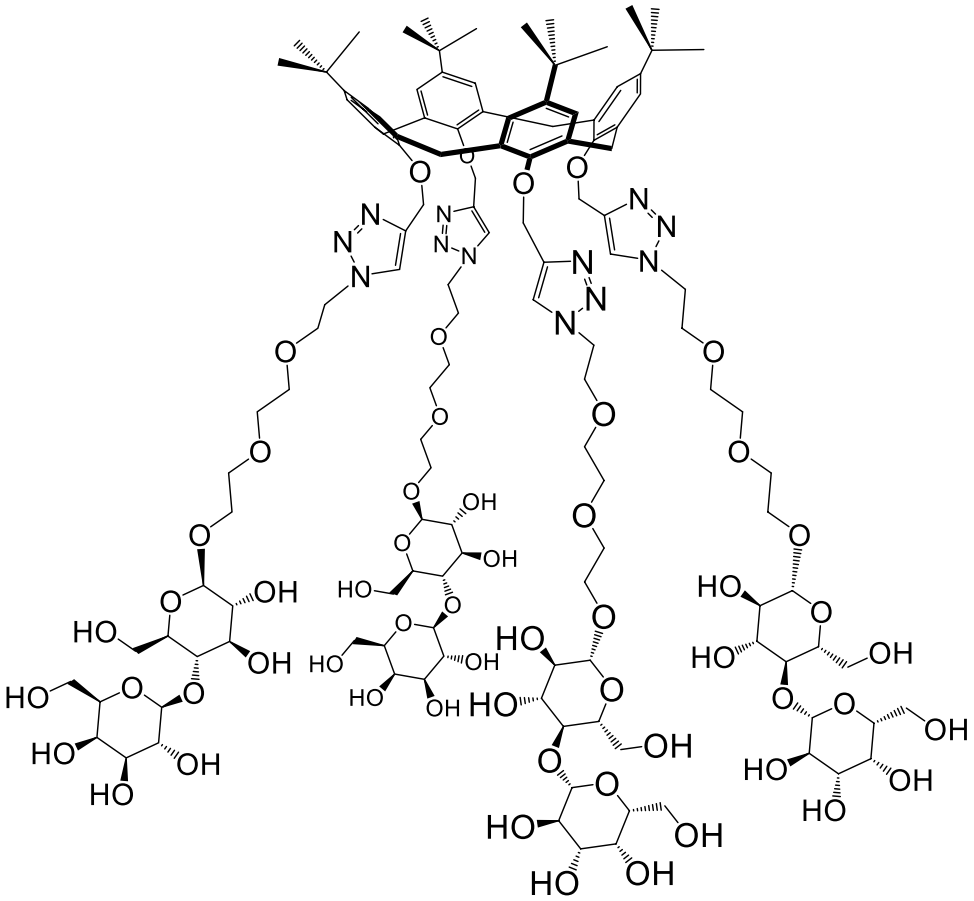
With the idea to mimic the activity of antibacterial peptides with amphiphilic structures for binding to lipopolysaccharide (LPS), Mayo and coworkers in 2006 [34] reported a novel small, non-peptidic calix[4]arene-based molecule as helix/sheet topomimetic with amphipathic surface topology (Fig. 19). It can effectively bind to and neutralize lipopolysaccharide (LPS) endotoxin (IC_{50}s = 0.04–1.5 μM) from Gram-negative bacterial membranes (i.e., *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Salmonella typhimurium*), via electrostatic and hydrophobic interactions between positively charged residues of the topomimetic binder and negatively charged groups on the lipid A component of LPS, in vitro as well as in vivo to combat LPS-induced septic shock in mice as a novel antiseptic agent. The presence of t-butyl groups on the hydrophobic face of the calix[4]arene scaffold is essential and increases inhibition activity significantly. The presence of four positively charged guanidinium groups promotes broad spectrum activity of compound.

Toll-like receptor 4 (TLR4) is a LPS sensor and fundamental factor in leading to septic shock. One of the main strategies to block abnormal TLR4 signaling in bacterial sepsis is based on using molecules that compete with endotoxic LPS in binding to its target sites. According this background, Casnati and his coworkers in 2017 reported a new fully functionalized amphiphilic guanidine-calix[4]arene (Fig. 20) with significant (IC_{50} = 0.7 μM) inhibition activity for LPS-Stimulated TLR4 signal in HEK human and murine cells. Briefly, this calix[4]API as a new inhibitor binds directly to the certain proteins (receptors) in competition with LPS [35].

Calix[4]API-based anti-myotonic agent

Another strategy used for calixarene protein binding is the stoppering of lipophilic cavities. The aromatic backbone of conical calix[4]arenes indeed offers an external lipophilic surface suitable to penetrate the apolar cavities/channels of proteins. This promising approach was recently followed by Nasuhi Pur and his coworker in 2019 [36], for reporting a new calix[4]API as a cyclic tetramer of mexiletine (namely calixmexitil, Fig. 21) with amplified (tenfold) in vitro anti-myotonic to respective monomeric, mexiletine in electrophysiological tests for blocking sodium channels in use-dependent manner in single skeletal muscle fibers of frog. The calix[4]arene structure decorated by four 2-aminopropoxy at the lower rim of the scaffold. The experimental results exhibited an amplified (tenfold) potency in producing phasic block as an indication of the anti-myotonic activity and improved (threefold) potency in producing use-dependent block for the cluster (calixmexitil) in relation to respective constitutive monomer (mexiletine). The potency in producing phasic block and use-dependent block are two

Fig. 18 Calix[4]API-based trypanocidal agent



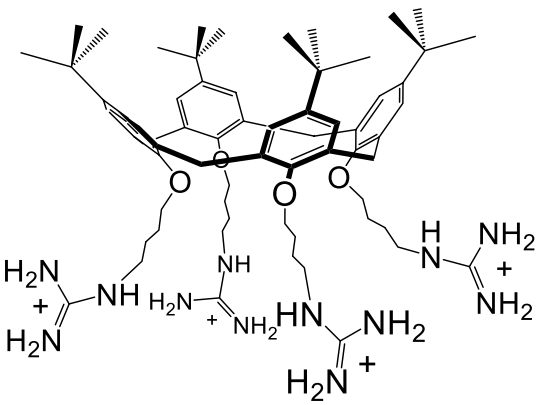


Fig. 19 Calix[4]API-based antiseptic agent

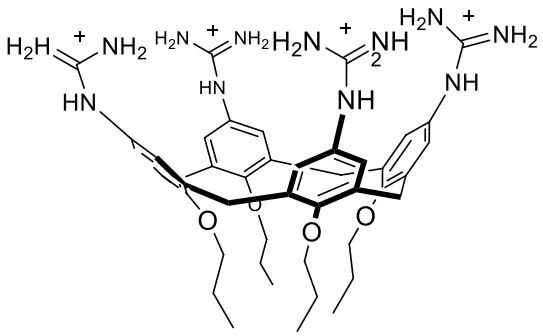


Fig. 20 Calix[4]API-based antiseptic agent

main factors to describe dose range, drug affinity, and side effects of an anti-myotonic agent. Therefore, with regards to mexiletine, calixmexitil with the improved factors can be considered as a "selective" anti-myotonic agent with low dose range. These improved biological effects are maybe ascribable to improved interaction of four impacted units of the calix[4]API in facial disposition with the sodium channels' structure in skeletal muscle fibers.

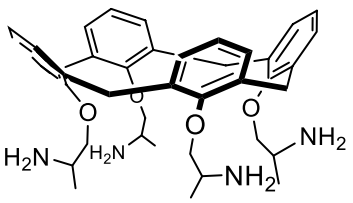


Fig. 21 Calix[4]API-based anti-myotonic agent

Conclusions

In summary, the present short-review covers the structures and biological features of 25 novel facial, conical, and symmetrical fully functionalized calix[4]arene-based APIs (calix[4]API-s), reported in the last two decades. These cyclic tetramers can be considered as potential therapeutic agents and can compete with reference API-s. Structural studies of these molecules could pave the way for the synthesis of similar structures to achieve more effective APIs than established types.

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