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Exploring the Expanding Frontiers: The Promising Role of Supramolecules in Advancing Cancer and Infectious Disease Therapy

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ABSTRACT

The use of calixpyrrole derivatives as potential anticancer and antibacterial agents has recently gained significant attention. We summarise recent advances in the design and production of calixpyrrole-based compounds as well as their biological actions against cancer and bacterial cells, in this overview. The structure-activity relationships (SAR) of these compounds and their mechanisms of action are discussed, highlighting their potential as therapeutic agents. Furthermore, we discuss the challenges and opportunities associated with the development of calixpyrrole-based agents as effective anticancer and antibacterial drugs. Overall, this review provides valuable insights into the development of novel calixpyrrole-based compounds with potent anticancer and antibacterial activities, which could have the way for the development of new therapeutics with improved efficacy and reduced toxicity.

Keywords: Calix[4]pyrrole, Anticancer agents, Antibacterial agents, Ion-pair receptor, Apoptosis.

INTRODUCTION

Cancer and bacterial infections remain significant public health challenges worldwide. Cancer is a complicated and diverse illness defined by uncontrolled cell growth and proliferation that can infiltrate and spread to other region of the body. Despite advances in diagnosis and treatment, many forms of cancer remain difficult to cure. Chemotherapy, radiation therapy, and surgery are the mainstay of cancer treatment, but these treatments often have severe side effects and may not be effective in all cases[1,2]. Moreover, bacterial infections continue to be a major global health concern, especially with the rise of antibiotic-resistant strains. In recent years, there has been a surge of interest in developing novel cancer and bacterial infection therapies that can target particular cells or bacteria while leaving healthy cells alone[3]. One approach is to use natural or synthetic compounds that have anti-cancer or antibacterial activity[4,5]. The ability to selectively target cancer cells or bacteria while sparing healthy cells, high binding affinity to cancer-specific targets or bacterial enzymes, lipophilicity, which can improve the drug's ability to penetrate cellular membranes and reach the target site, and biological stability to ensure that an adequate concentration of the drug reaches the target location[6-9].

Natural substances with anti-cancer and antibacterial action include curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG).[10–14] However, the development of synthetic compounds with anti-cancer and antibacterial activity is also an active area of research[15–18]. One such class of synthetic compounds that has shown promise in both cancer and antibacterial research is calixarenes. Calixarenes are cyclic organic molecules that have a three-dimensional basket-like structure. They were first synthesized in the 1940s, but their potential as anti-cancer and antibacterial agents was not explored until much later. Calixarenes can be modified with heteroatoms, resulting in a variety of heterocalixarenes, or they can contain mixed heteroatoms, resulting in heteracalixarenes[19,20]. Calixarenes have a unique structure that allows them to selectively bind to cancer cells or bacteria and induce apoptosis or cell death in these cells. They can cause apoptosis through a variety of pathways, including caspase activation, disturbance of the mitochondrial membrane potential, and inhibition of the NF-B pathway. Several studies have investigated the anti-cancer and antibacterial activity of calixarenes in various types of cancer and bacterial infections. They have shown potential in slowing cancer cell development and killing microbes, including antibiotic-resistant strains[21, 22]. Calixarenes also have the potential to enhance the efficacy of other anti-cancer or antibacterial agents[23]. Their structure enables them to attach to cancer cells specifically and cause apoptosis, or programmed cell death[24,25]. Apoptosis is a natural process that occurs in cells to eliminate damaged or abnormal cells, and it is an important mechanism for controlling cancer growth. Calixarenes can induce apoptosis by several mechanisms, including activation of the caspase pathway, disruption of the mitochondrial membrane potential, and inhibition of the NF-B pathway[26,27].

Several studies have been conducted to explore the anti-cancer action of calixarenes in different cancer types, including breast, lung, and colon cancer[28]. In one study, a group of researchers synthesized a series of calixarenes and tested their activity against human breast cancer cells. They found that some of the calixarenes were able to prevent breast cancer development cancer cells and induce apoptosis in these cells. Another study investigated the activity of calixarenes against human colon cancer cells and found that the compounds were able to inhibit the growth of these cells and induce apoptosis through the caspase pathway[29,30]. In addition to their ability to induce apoptosis, calixarenes also have the potential to enhance the efficacy of other anti-cancer agents. A research, for example, looked at the action of a mixture of calixarene and cisplatin, a widely used chemotherapy medication, against human lung cancer cells. The researchers discovered that the combination was more successful than either calixarene or cisplatin alone at inhibiting the development of lung cancer cells.[31]

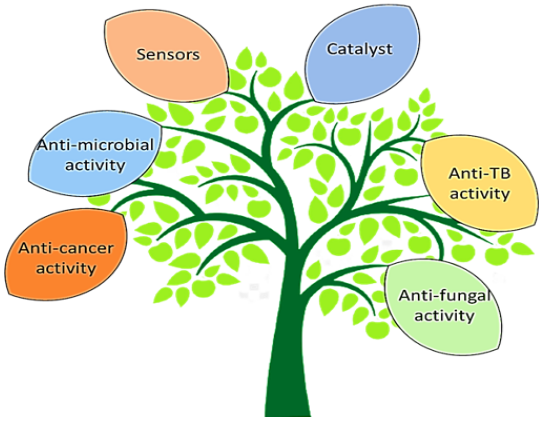

Fig. 1. Different applications of functionalized calix[4]pyrrole

Calix[4]pyrroles and Anti-cancer Activity

Calix[4]pyrrole is widely used in the fields of sensor for detecting metal ions, as a host for encapsulating guest molecules[32], and as a catalyst for organic reactions[33,34]. It also has potential applications in drug delivery, and range of therapeutic activities. It has been studied for its potential therapeutic activity, particularly as an anticancer agent[35–37]. Calix[4]pyrrole is a potential option for further research as an anticancer drug due to its ability to cause apoptosis (programmed cell death) in cancer cells when CK2 is inhibited.[38,39] The existence of nitrogen atoms in the calixpyrrole ring structure causes this selective binding, which can form hydrogen bonds with the amino acid residues on the surface of cancer cells[40,41]. This selective binding makes calixpyrroles potentially less toxic to healthy cells, which is a major advantage over many existing chemotherapeutic agents that can cause significant damage to healthy cells. Overall, calixpyrroles have several properties that make them attractive as potential anticancer and antibacterial agents. Their ability to selectively bind to cancer cells,

induce apoptosis, cell growth inhibition of bacterial cell making them promising candidates for further research in this field.

Calix[4]pyrrole based Anti-cancer agents:

Marta and colleagues synthesized several derivatives of calix[4]pyrrole and tested their cytotoxicity on A549 cancer cells. They found that one of the derivatives, meso-(p-acetamidophenyl)-calix[4]pyrrole Fig. 2, Structure 1, exhibited the highest cytotoxicity, which was attributed to the combination of three structural elements: (i) a single acetanilide unit at (ii) a meso-position of (iii) a complete calix[4]pyrrole structure. The researchers proposed a mechanism in which the calix moiety binds non-covalently with phosphate, bringing the acetanilide unit of the calix in close proximity to the nucleobase(s) in a spatial arrangement similar to their previous study. In-silico tests showed that compound 1 function as a minor groove binder by bringing the amide group near to an adenine N3 atom. According to the molecular docking modeling, the calixpyrrole unit may help with the active transport of the alkylating acetanilide component to the minor groove, resulting in genotoxic damage and cell mortality. Overall, these data indicate that the synergistic action of two components of compound 1 causes genotoxic damage that result in cancer cell death.[42,43]

Sessler's group discovered that two pyridine diamide-strapped calix[4]pyrroles, 2 and 3 Fig. 2, Structure 2 & 3, can transport chloride anions and sodium cations. In both liposomal models and cells, raising intracellular chloride and sodium ion concentrations promotes cell demise. They also discovered that the transporter-mediated apoptosis caused by these compounds is reliant on the presence of both extracellular chloride and sodium ions, as well as the presence of active sodium channels. Flow cytometry analysis of cell size showed that cells treated with 2 and 3 in HBSS shrank significantly. They also discovered that these transporters raise intracellular sodium chloride concentrations, increase cellular ROS levels, trigger mitochondrial cytochrome c release, and activate caspases[46]. Park *et al.,* reported in a recent research that the ion transporter octafluorocalix[4]pyrrole Fig. 2, Structure 4 causes apoptosis by increasing cell sodium and chloride concentrations, while also inhibiting autophagy by interrupting lysosome function. These findings suggest that calix[4]pyrroles have potential as ion transporters and could be explored further as a novel approach to inducing apoptosis and inhibiting autophagy in cancer cells[44].

Rosamaria and colleagues investigated the molecular mechanisms underlying the inhibitory action of a calixpyrrole derivative, C4P Fig. 2, Structure 5, on GPER activation. Their findings show that C4P 5 acts as a GPER antagonist in breast tumor cells and cancer-associated fibroblasts (CAFs) from breast cancer patients by inhibiting GPER-activated signals. Interestingly, when exposed to estrogen, C4P 5 becomes extremely selective for GPER without interfering with oestrogen receptor-dependent reactions. These findings emphasise the promise of calixpyrrole derivatives as breast cancer therapeutics and provide significant insights into the processes underpinning their anti-tumor actions.[45]

Megharaja *et al.,* discovered promising anticancer activity in coumarin analogues of dipyrromethane and porphyrin derivatives. Compounds Fig. 2, Structure 6a and 6b showed remarkable activity *in vitro*, with GI50 values of around 1.0 μM and <1.0 μM, respectively, across a wide range of cell lines. After further evaluation at five dose levels, compound 6a showed enhanced antiproliferative activity and have been referred for advanced study by the Biological Evaluation Committee of NCI. These findings hold potential for the development of novel and effective anticancer therapies[46].

Kongor *et al.,* investigated the cytotoxicity of a calix[4]pyrrole compound, meso-tetra (methyl) meso-tetra (3-methoxy 4-hydroxy phenyl) calix[4] pyrrole HMCP Fig. 2, Structure 7, and its hydrazide derivative, MCPTH Fig. 2, Structure 8, against two cancer cell lines. They proposed that HMCP, which contains more hydrogen bond donor functional groups than MCPTH, is more potent in its anticancer activity due to the strong donor properties of halogen acids, OH groups, and NH groups. The authors suggested that calixarene-based compounds may act through a unique mechanism and further research is necessary to fully understand their mode of action[47]. Further they reported the synthesis of calix[4]pyrrole tetrahydrazide stabilized gold nanoparticles (MCPTH-AuNPs) and their potential as a cytotoxic agent against MCF-7 cancer cells[48].

The IC_{50} value for the nanoparticles was found to be 25.69 µg/mL, indicating moderate anticancer activity. The study also suggests that the cytotoxic effects of calix conjugated gold nanoparticles can be linked to anticancer activity and can be used as a potential source of anticancer drugs. Comparisons with other gold nanoparticles show that the cytotoxicity profile depends on the nature of cell types and their chemical composition. Overall, the study suggests that calix[4]pyrrole tetrahydrazide stabilized gold nanoparticles have potential as a cytotoxic agent against MCF-7 cancer cells.

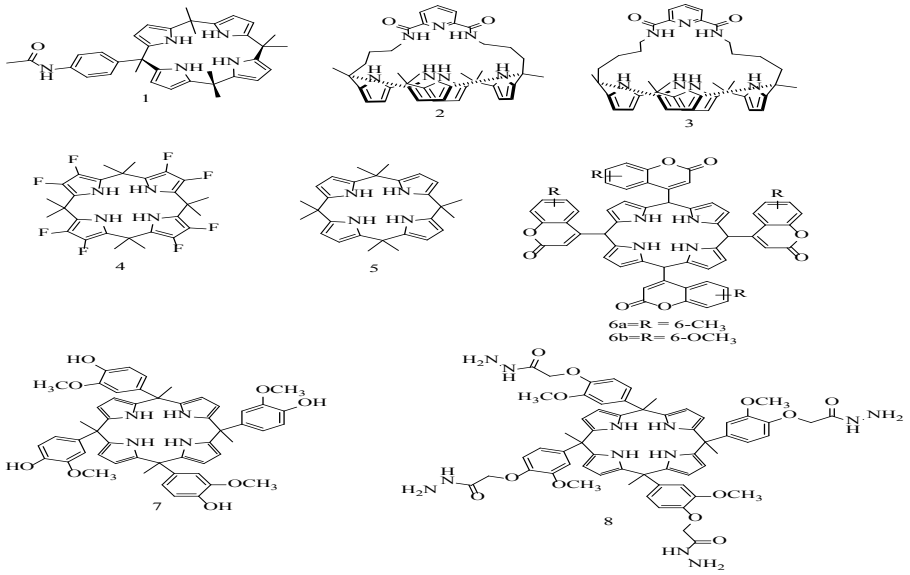

Fig. 2. Calix[4]pyrrole derivatives, evaluated for their anti-cancer activity

Calixpyrrole based Antibacterial agents

Kongor *et al.,* reported the potential biological applicability of CPTH-PdNPs as an antimicrobial agent[49]. The nanoparticles exhibit potential antimicrobial activity against gram-negative bacteria, particularly *E.coli*, as shown by the micro-broth dilution method. The minimum inhibitory concentration of CPTH-PdNPs is determined and compared to the standard drug Ampicillin. The results suggest that CPTH-PdNPs can be formulated as a chemotherapeutic drug for the treatment of some entero-pathogenic *E. coli* infections. Overall, the article presents CPTH-PdNPs as a promising nanocatalyst with potential applications in both catalysis and biomedical fields. In addition, the authors use the micro-broth dilution technique to assess the antibacterial activity of CPTH with silver nanoparticles against different microorganisms such as *E. coli, P. aeruginosa, S. aureus*, and *B. subtilis*[55]. The minimal inhibitory concentration (MIC) of CPTH-AgNPs is found and compared to standard medicines like ampicillin and chloramphenicol. According to the findings, CPTH-AgNPs suppress the development and multiplication of the studied *Gramme-negative* bacteria, especially *E. coli*, more effectively than *Gramme-positive* bacteria. Overall, the findings indicate that CPTH-AgNPs can be used as an antibacterial agent, with possible uses in medical equipment and pharmaceutical therapies.

CPTH Fig. 3, Structure 8 is a common component in both studies, and it could have played a significant role in the antibacterial activity of both silver and palladium nanoparticles. The use of CPTH as a stabilizing agent for the synthesis of silver and palladium nanoparticles could have contributed to their antibacterial activity by enhancing their stability and biocompatibility. Moreover, the presence of CPTH on the surface of the nanoparticles may have created a positively charged environment which could have caused damage to the bacterial cell membranes. This could explain the observed antibacterial activity of both CPTH-AgNPs and CPTH-PdNPs against various microorganisms[50,51]. Overall, the use of CPTH in both studies could have played a significant role in the antibacterial activity of the synthesized nanoparticles, it is important to note that the antibacterial activity of nanoparticles can be influenced by several factors, such as particle size, shape, surface charge, and coating, and further studies are needed to optimize the antibacterial properties of both types of nanoparticles for various applications.

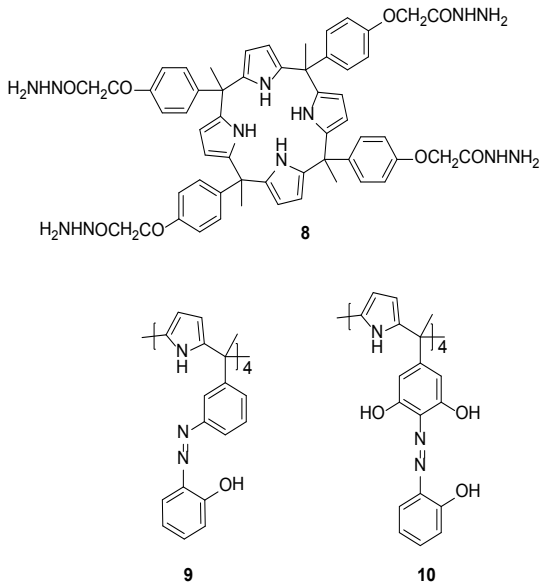

Fig. 3. Calixpyrrole derivatives as antibacterial agents

Using the paper disc technique, Jain *et al.,* examined the antibacterial activity of eight azocalix[4]pyrrole dyes Fig. 3, Structure 9 & 10 against *Escherichia coli* and *Staphylococcus aureus*[58]. All compounds were made in two concentrations, and chloramphenicol was used as a standard for biological research. The dishes were then incubated at room temperature for 18 h and the zone of inhibition (diameter) was measured in each instance. The results showed that among the various azocalix[4] pyrrole dyes, 9 and 10 had the most effective antibacterial activity against these microbes, which could be attributed to the presence of a -OH group ortho to the azo, allowing for easier attack on the cell of microbes than other azocalix[4]pyrrole compounds.

Summary and outlook

The development of effective anti-cancer agents is of critical importance in the fight against cancer. The compounds reviewed in this article, which are based on the calixpyrrole scaffold, represent a promising avenue for the development of novel anti-cancer agents. The unique structure of calixpyrrole allows for selective binding to cancer cells and induction of apoptosis, which is a key mechanism for the elimination of cancer cells. Moreover, the selected calixpyrrole based compounds have demonstrated potent anti-cancer activity against a range of cancer types, including breast, lung, and liver cancer. These compounds may also have the potential to enhance the efficacy of existing anti-cancer therapies.

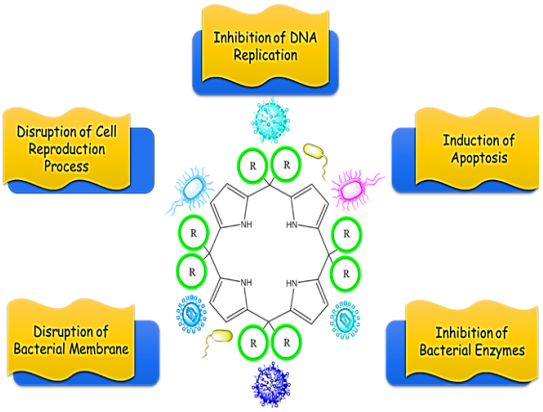

Fig. 4. Different mechanisms of action for antibacterial and anticancer activity of calixpyrrole based derivatives

The calixpyrrole scaffold has also shown promising potential as a basis for the development of antibacterial agents, in addition to its anti-cancer properties. The unique structure of calixpyrrole allows for selective binding to bacterial cells and disruption of essential cellular processes, leading to bacterial death. Some calixpyrrole-based compounds have demonstrated potent antibacterial activity against a range of pathogenic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, which are known to cause difficult-to-treat infections.

Overall, the potential of calixpyrrole based compounds in therapeutic agents is an exciting area of research with significant implications for the development of effective treatments. Further research is needed to fully understand the mechanisms of action and optimize the efficacy and safety profiles of these compounds. Nonetheless, the potential of calixpyrrole based compounds in anti-cancer and anti-bacterial therapy represents a promising approach towards achieving improved outcomes for cancer patients.

CONCLUSION

In conclusion, the studies on calixpyrrole-based anticancer and antibacterial agents have shown promising results in terms of their potential as effective treatments for cancer and bacterial infections. The unique properties of calixpyrroles, such as their ability to selectively bind to target cells and their structural versatility, make them attractive candidates for drug development. Furthermore, the studies have highlighted the importance of careful design and optimization of calixpyrrole-based compounds in order to enhance their efficacy and selectivity, while minimizing toxicity. Future research in this field will be crucial in furthering

our understanding of these compounds and their potential as therapeutic agents for various diseases.

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Conflict of interest

The author declare that we have no conflict of interest.

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