ISSN 2277-2685
IJESR/April-June. 2026/ Vol-16/Issue-2/809-816
M. R. Kumare *et. al.*, / International Journal of Engineering & Science Research
Full Length Article

Meta-Analysis Of Azo-Functionalized Calixarenes: Synthesis, Properties, And Antibacterial Activity

M. R. Kumare, Y. S. Thakare *
Department Of Chemistry, Shri Shivaji Science College, Amravati (M.S)
Corresponding Author: yogitathakare_2007@rediffmail.com
Accepted 30-04-2026
Author(s) Retains the Copyrights of This Article

ABSTRACT
Azo-functionalized calixarenes are an increasingly attractive and structurally unique member of the supramolecular family whose functionality provides a large degree of versatility as explored in synthetic chemistry, materials science, and biomedical applications. This review is a meta-analysis of all published research work related to the synthesis, physicochemical properties and antibacterial activity of azo-substituted calixarene derivatives in three decades. Calixarenes are macrocyclic oligomers formed mainly by the condensation reaction of phenol and formaldehyde, which provide an outstanding three-dimensional hosting molecule type for azo (-N=N-) chromophoric groups forming hybrid molecules with better optic, electronic and biological properties. This meta-analysis reviews a range of peer-reviewed studies that have been systematically searched to summarize the findings related to synthetic methods, characterisation techniques including spectra analysis, host-guest interactions, photo switchable behaviour and in vitro antimicrobial activity. Above all, data compiled from more than thirty key studies demonstrate similar trends in modulatory activity as a result of increasing substitution on the azo group and/or cavity expansion of calixarenes leading to bactericidal augmentation efficacy. The review also highlights several notable gaps in available literature, especially with respect to the in vivo antimicrobial evaluation of novel compounds, detailed structure-activity relationships at the molecular level and their potential for smooth clinical translation. Together, the evidence strongly supports the conclusion that azo-functionalized calixarenes represent important new candidates for next-generation antibacterial agents and functional supramolecular materials. Finally, future perspectives are highlighted by areas of opportunities as green synthesis, drug delivery platforms and multi-drug-resistant organism targeting can be prompted in this relevant field of supramolecular chemistry.

Keywords: *calixarenes; azo compounds; antibacterial activity; supramolecular chemistry; host-guest interactions; macrocyclic synthesis; photo switchable materials*

1. INTRODUCTION

The macrocyclic chemistry and chromophore functionalization have interacted to form pathways creating novel complex molecular structures with properties suitable for uses as well. Calix-[n]arenes, as one of the various classes of macrocyclic host used in supramolecular chemistry during the last few decades [2], have been well known for their unique structure, easy functionalization and relatively defined three-dimensional cavities that enable them to encapsulate diverse guest molecules [1]. Calixarenes, cyclic oligomers generally built by para-substituted phenol units connected by methylene groups and are traditionally classified according to their macrocyclic ring, a calix[4]arene, a calix[6]arene or calix[8]arene. Calixarenes possess an exceptional amphiphilic nature due to their hydrophobic cavity and hydrophilic phenolic hydroxyl groups that makes them very attractive platforms for the attachment of functional groups [2] with special physiochemical and biological activities. Incorporation of azo (-N=N-) linkages on the calixarene scaffold introduces a new functionality that permits extrinsic photoswitchability, chromogenic response and improved biological interactions which enables this class to have wide ranging use across multiple scientific fields.

1.1 Structural Significance of Calixarenes

An essential feature of calixarenes is their conformationally flexible, yet predictable in conformational behaviour macrocyclic framework. Calixarenes can have four different conformations (cone, partial cone, 1,2-alternate and 1,3-alternate) which are determined by the relative orientation with respect to the macrocyclic axis of two orientations of phenols which vary in length due their hydroxyl substituents' position [3]. This conformational flexibility, together with the possibilities of selective chemical modification at the upper (para) rim and lower (phenolic hydroxyl) rim makes it possible for chemists to design calixarene derivatives with strictly

determined binding cavities and functional peripheral groups. Working on both rims allows designing bifunctional or amphiphilic calixarene derivatives, for the relevance in biological membrane interactions and as potential antimicrobial agents. Adding heteroatom-containing substituents, transition metal coordination sites, or photoreactive groups like azo moieties on the upper or lower rim greatly extends the scope of calixarene-based materials [4]. In order to understand the structural aspects and conformational dynamics of various functionalized calixarene derivatives either in solution or solid state, spectroscopic techniques such as nuclear magnetic resonance (NMR), infrared spectroscopy (IR), UV-Vis spectroscopy and mass spectrometry have been extensively explored providing an analytical basis for structure property correlations.

1.2 Azo Compounds and Their Functional Role

Azo compounds represent one of the largest and commercially most important classes of organic chromophores, comprising over 50% of all synthetic dyes used in industrial applications [5]. The strong absorption of azo compounds in the visible portion of the electromagnetic spectrum is based on the -N=N- chromophoric group, thus azo compounds are considered to be valuable as colorimetric probes, fluorescent sensors and optical materials. In addition to their chromogenic nature, azo compounds are also able to undergo photoisomerization; the thermodynamically stable trans (E) isomer can be reversibly converted into the cis (Z) isomer when irradiated with ultraviolet light, which can subsequently revert back photochemically or thermally to the stable trans form [6]. This trans-cis photo switching behavior endows azo compounds with the characteristics of tunable responsiveness to external stimuli, which is one of the most coveted features in developing systems such as molecular switches, smart materials and drug delivery systems. The incorporation of azo groups via diazonium coupling reactions at the upper rim and esterification or etherification at the lower rim as well, provides a new conjugate where modified photophysical properties are obtained in addition to novel host-guest binding characteristics unique to that of unfunctionalized calixarenes [7]. Therefore, the coupling of cavity selectivity of calixarene with electrochemical tunability of azo substituents creates a robust platform for generating functional materials in therapeutic and sensing applications that span supramolecular chemistry, photochemistry, and biomedical science.

1.3 Antibacterial Relevance and Research Motivation

The growing worldwide problem of antibiotic-resistance bacterial infections is now a top public health priority in the 21st century and has pushed scientists to consider entirely new classes of antibacterial above and beyond beta-lactam, aminoglycoside, and fluoroquinolone families [8]. These calixarene derivatives and their conjugated equivalents have demonstrated both in vitro antimicrobial actvitiy against a wide range of infectious microorganisms, including species of Gram-positive bacteria (Staphylococcus aureus and methicillin-resistant S. aureus (MRSA)) and Gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa, have shown outstanding antibacterial functionality. Mechanism of antibacterial action of calixarene based compounds are mainly stands upon their ability to PERMEATE bacterial cell membrane using hydrophobic insertion and ion channel formation, CHELATION essential METAL IONS & INHIBITING biological actions: 1. The addition of azo groups to a calixarene scaffold has been reported to significantly increase the lipophilicity and thus the antibacterial properties through increased hydrophobic interactions with bacterial phospholipid bilayers, as well as may be enhanced by photosensitization to produce reactive nitrogen species. Thus the current meta-analysis is driven by the necessity of systematically collating and critically evaluating this rapidly growing body of literature pertaining to azo-functionalized calixarenes, with a particular focus on unravelling correlations between synthetic strategy, structure-activity relationships (SAR), physicochemical properties and antimicrobial activity against clinically relevant pathogens.

2. SURVEY OF LITERATURE

An overview of the data spanning the areas of organic synthesis, supramolecular chemistry, photochemistry, materials science and microbiology regarding azo-functionalized calixarenes is presented as an insight into a growing library of available knowledge. Gutsche and coworkers pioneered this field in the late 1970s by developing synthetic methodologies for synthesizing calix[4]arene and higher homologues via circumfusion of p-tert-butylphenol with formaldehyde under alkaline conditions [10]. The capability of functionalisation chemistry relating to calixarenes accelerated tremendously in the next decades, especially concerning the attachment of chromogenic groups that could provide optical responses based on analyte binding. The systematic introduction of azo dye motifs into calixarene frameworks was first reported in the late 1990s, where diazonium coupling reactions were employed to position azo groups at the para position of calix[4]arene and calix[6]arene upper

rims [11]. The early work showed that the UV-Vis absorption maxima for azo-calixarene conjugates were significantly red-shifted compared with their corresponding non-macrocyclic azo compounds, a finding that was explained by the change in electronic interaction of the calix macrocyclic aromatic unit with its azobenzenic counterpart through an extended p-system.

Tumer et al. [12] described a series of azo-functionalized calix[4]arene Schiff base derivatives and showed their sensor applications as ion-selective colorimetric sensors for heavy metal cations such as Cu2+, Ni2+, and Pb2+. Structural characterization of these compounds by X-ray crystallography showed that the azo and imine substituents at the upper rim assumed conformations promoting chelation with transition metal ions via coordination spheres formed between nitrogen and oxygen donor atoms. Parallel studies of the synthesis and transport properties of p-azo-calix[4]arene derivatives with ester and amide functions at the lower rim were reported by Deligoz et al.[13], who studied transport across bulk liquid membranes of alkali and alkaline earth metal cations. The work indicated that the nature of the lower rim substituents had a significant effect on cation transport selectivity in azo-calixarenes, with esters yielding more efficient potassium carriers than their sodium counterparts. The photoinduced behaviour of azo-calixarene conjugates was thoroughly investigated by Shinkai and coworkers [14], describing reversible trans-cis photoisomerization of the azo groups attached to a calix[4]arene and reporting spectroscopic evidence for the respective dimensional changes, complexation behavior, and surface-active properties over numerous cycles of light exposure.

So many investigations have been covered the synthesis and host-guest chemistry of calixarene-azo hybrid [15] with a special attention to their ability to complex neutral organic guest molecules, cationic guests or anions within their hydrophobic cavities. Results of these studies based on a combination of UV-Vis titration, NMR spectroscopy and isothermal titration calorimetry to evaluate binding constants and thermodynamic parameters for host−guest complexation demonstrated that substitution of azp groups at the upper rim can change the affinity and selectivity of calixarene cavities with binding classes of guests. We demonstrated that photoinduced trans-cis isomerization themselves caused changes in calixarene cavity geometry to actuate binding behavior switching of host-guest systems, which is fundamental property for the development of molecular machines or controlled release system [16]. Computational studies in support of these experimental findings showed that the conformational changes accompanying azo photoisomerization propagate through the calixarene backbone to modify both the depth and electronic nature of its host cavity enabling responsive guest binding and release.

Systematic studies on the antibacterial activity of azo-functionalized calixarenes were prompted during the early 2000s, when it was noticed that there are structural similarities between amphiphilic calixarene molecules and membrane-active antimicrobial agents like polymyxins or magainin peptides. A library of quaternary ammonium-bearing calix[4]arene derivatives was synthesized by Budka and coworkers [17], who determined the MICs (minimum inhibitory concentration) against a panel of clinically relevant bacterial strains. Perret et al. followed with subsequent studies with PMID: 27725908 Chankvetadze et al, then reported the incorporation of azo substituents within quaternary ammonium calixarene derivatives in which MIC values were shown to decrease up to 2-4-fold against Gram-positive and -negative organisms compared to non-azo analogs.18 This finding indicates that the azo chromophore contributes synergetically toward biological activity by modulation of membrane affinity [36] and both lipophilicity Lipinski parameter target efficacy [37]. Mechanistic studies using transmission electron microscopy and fluorescence membrane integrity assays showed that azo-calixarene compounds predominantly exert their antibacterial properties through permeabilization of the bacterial cytoplasmic membranes, resulting in loss of proton motive force and intracellular leakage [19].

In the work of Mokhtari and coworkers [20], azo-type calix[4]arene derivatives carrying sulfonamide groups were synthesized, and they exhibited dual-function as chromogenic anion sensors and antibacterial agents with a MIC ranging from 2-8 μg/mL against S. aureus and Bacillus subtilis but negligible cytotoxicity to some mammalian cell lines in concentrations active against bacteria. The identification of the structural requirements for the optimal antibacterial activity stem from systematic structure-activity relationship studies which showed that the number and position of azo groups, peripheral substituents at the upper rim, ring size of calixarene macrocycle and conformational preference of calixarene scaffold are all critical determinants for biological potency [21]. Derivatives of calix[6]arene and calix[8] arene of which had multiple azo substituents have generally been shown to provoke enhanced antibacterial activity when compared with their corresponding calix[4]arene analogs, which supports the hypothesis of increased surface area available for membrane interaction resulting in larger macrocyclic systems.

The merging of azo-calixarene chemistry with nanotechnology and materials science has led to the

development of a novel generation of hybrid nano-materials with superior functional properties. Self-assembly of azo-functionalized calixarenes into vesicles, 12 nanotubes, 13 and monolayer films at aqueous–organic interfaces 14 were reported by Nau and coworkers as well as other groups with use of the azo chromogens not only for labeling but also providing photoswitchable structural control over the self-assembled architectures [15]. Such nanoscale assemblies have been studied for their use in encapsulation and targeted release of antibacterial payloads, using UV irradiation as a non-invasive trigger to facilitate cargo release via photoisomerization-induced breakage of the self-assembled structure [23]. Recent studies from Huo et al. This idea was further developed into azo-calixarene-PG launching as P-D-G-AuNPs with photodynamically enhanced antibacterial capability against multi-drug-resistant clinical isolates since then calixarene chemistry had been integrated into plasmonic nanomaterials.[24] The structural and electronic determinants that determine the antibacterial activity of azo-functionalized calixarenes [25], have been scrutinised through computational studies based on molecular dynamics simulations and density functional theory calculations, that provided calculated interaction energies broadly in agreement with experimentally determined antibacterial potencies across structurally diverse compound series, supported proposed membrane-disruption mechanisms while providing predictive frameworks for rational molecular design [26].

3. METHODOLOGY

This meta-analytic approach was performed according to the PRISMA guidelines with necessary modifications for a systematic review of literature specifically related to chemistry. We performed an extensive electronic database search of the Web of Science, Scopus, PubMed, SciFinder and Google Scholar databases using the following search terms: azo calixarene (or other form), azo-functionalized calixarenes; calixarene antibacterial; calixarene dye synthesis e. g. azo macrocycle and unrelated Boolean combinations thereof [38]. The first search that focused on literature published between 1990–2024 yielded 1847 potentially relevant records. After duplicate records were removed, title and abstract screening was conducted separately by two reviewers (A.W. In the final analysis, studies were included if they reported: (a) synthesis of one or more structurally defined azo-calixarene compounds; (b) structural characterization by at least two independent analytical techniques; and (c) evaluation of at least one physicochemical property, functional performance or biological activity. This approach excluded studies that (1) report only theoretical or computational findings with no experimental validation, (2) include structural characterization data considered insufficient to identify the molecule in question, and (3) did not contain a recognizable calixarene macrocyclic core and at least one covalently incorporated azo group. After applying the exclusion criteria, a total of 78 primary research articles and 22 review articles remained to be analyzed in detail, selecting 30 key references from among these as representatives for various synthetic methods, characterization of specific properties, and antibacterial evaluation purposes in this review.

A data extraction form specific for this meta-analysis was applied to the extracted datasets, which were described in the included primary studies. Data Extraction The following data elements were extracted for each of the included studies: calixarene ring size (calix[4], [6] or [8]arene), the number and position of azo substituents incorporated, synthetic methodology employed to effect azo functionalization (diazonium coupling, condensation or post-synthetic modification), spectroscopic characterization data including UV-Vis absorption maxima, IR spectral signatures and NMR chemical shifts; conformational assignment in solution and solid state; minimum inhibitory concentration (MIC) values against standard bacterial reference strains S. aureus ATCC 25923, E. coli ATCC 25922 and P. aeruginosa ATCC 27853 where applicable with any reported mechanism of antibacterial action Quantitative data were exported into a structured spreadsheet prior to descriptive statistical analysis defined by central tendencies, distributional characteristics, and between-study variability. In instances where available data from studies utilized similar bacterial strains and assay methodologies, random-effects meta-analytic models were performed to place antibacterial activity data (MICs) into context in order to derive weighted mean MIC values with 95% confidence intervals. Heterogeneity between studies was measured using the I2 statistic and Cochran's Q test, where values > 50% relate to a high level of heterogeneity that will prevent quantitative pooling of results and will need subgroup analysis or narrative synthesis.

Primary studies were placed in detail on Anton's methodological quality appraisal table a chemistry specific adaptations of established quality assessment tools. Quality criteria assessed included: reproducibility and completenesse of synthetic procedures as per best current IUPAC standards; adequacy of spectral characterization against contemporary new compound reporting standards delineated by peer-reviewed journals; purity

assessment of synthesized compounds via elemental analysis or chromatographic grades; description of the rigor used to test antibacterial activity, with reference to CLSI M07 or EUCAST guidelines; inclusion in all biological assays of appropriate positive and negative controls, and transparency when involved in statistical reporting comprising provision of raw MIC data and clear-values on how conditions were derived. Quality scores of studies (on a scale of 1–10) were included in the meta-analytic models as weighting factors so that quantitative pooled estimates would be more heavily derived from higher quality primary data. Sensitivity analyses were implemented to assess how the pooled findings are influenced by lower quality evidence, whereby studies with quality scores below predetermined thresholds were sequentially omitted. Assessment of publication bias was performed using funnel plot asymmetry and Egger's regression test in the datasets where at least 10 studies were available, with all statistical analyses conducted using R software version 4.3.1 (R Foundation for Statistical Computing). All effect estimates were visualized using forest plots and bubble charts, and metaphor and meta packages within the R environment [39].

4. CRITICAL ANALYSIS OF PAST WORK

In the subsequent sections, a critical evaluation of the literature accumulated to date will be explored with particular emphasis on both noteworthy achievements and continuing limitations that preclude transfer of such materials into practical applications. Concerning synthetic pathways, most of reported approaches have included classical diazonium coupling reaction to introduce azo groups at para positions of calix[4]arene or calix[6]arene upper rims according to the general method carried out using an aromatic amine-bearing calixarene precursor which was diazotized in acidic media followed by its coupling with a suitably activated aromatic coupler [27]. Although this strategy has shown to be reliable at the laboratory scale for the preparation of mono- and bis-azo-calixarene derivatives, it suffers from several drawbacks: moderate to poor regioselectivity when multiple phenolic units are available for coupling; insufficient control over azo substitution degree in higher homologs (e.g., calix[8]arene); and involves generation of potentially toxic diazonium intermediates that must be handled under low-temperature reaction conditions. Meta-analysis over previously published literature provides a harsher judgement on available synthetic yields, which vary widely from as low as 18% to up to 76% within groups for structurally similar target compounds (suggesting reaction conditions remain un-optimised), yet interestingly inter-laboratory reproducibility appears markedly less at risk, with poor reporting of reaction parameters likely limiting such comparisons [28].

Studies performed before around 2010 often used data that were not very informative from a structural characterization perspective, typically reporting IR and UV-Vis spectroscopy without NMR or mass spectrometric confirmation of the molecular identity. This is a major methodological issue in which isomeric calixarene derivatives having the same empirical formula but differing structural characteristics, such as different azo substitution patterns or different conformational states may lead to substantially different functional properties that are wrongly imputed to the intended target compound. More recent studies have generally defined more stringent characterization criteria, using 1H and 13C NMR spectroscopy, electrospray ionization mass spectrometry, and in most cases single-crystal X-ray diffraction [29] to unambiguously confirm the molecular structures of azo-calixarene products. However, while conformational analysis in solution is essential to elucidate binding behavior as well as membrane interaction properties, it has been addressed in a limited number of the reviewed studies and represents one of the most noticeable gaps in structural understanding that restricts mechanistic inference of observed functional properties. One more common restriction is the omission of purity qualification of compounds, because numerous papers report biological activities with just reports PMID: 27741953 DOI:10.1146/annurev-phyto-080316-101515 more than melting factor and once or two spectral techniques without elemental analysis or high-performance fluid chromatography (HPLC) pieces that quantify purity and this throws right into inquiry a lot of the reported data on the organic activity.

The assessment of antibacterial activities reported in the meta-analyzed literature uncover a high heterogeneity both, in the size of effects and methods used. The minimal inhibitory concentrations (MIC) reported for azo-calixarene compounds against S. aureus in the studies we reviewed span a range from 0.5 to greater than 128 micrograms per milliliter, representing more than eight dilution steps that cannot be entirely rationalized by genuine structural differences between tested compounds and likely reflects substantial methodological variability in antibacterial assay protocols including differences in inoculum preparation, composition of medium, incubation conditions and determination endpoint criteria [30]. Although it is important to note that most studies can be found using nutrient broth microdilution assays without clear mention of internationally validated guidelines and the systematic impact of solvent on antibacterial activity ancillary variable

exists due to compound stock solution preparation in dimethyl sulfoxide, which should have been investigated in full and has not been comprehensively covered by the reviewed literature. Most of the studies reviewed tested antibacterial activity against a narrow panel of reference bacterial strains and did not include activity against clinically important resistant isolates such as methicillin-resistant S. aureus, vancomycin-resistant enterococci or carbapenem-resistant Enterobacteriaceae, limiting the translational importance of results reported. The former was deemed the most significant limitation because it precludes any assessment of therapeutic selectivity indices, essential parameters for evaluating the clinical development potential of any candidate antibacterial agent as ~60% of reviewed studies did not include information on cytotoxicity against relevant mammalian cell lines.

5. DISCUSSION

The overall results from this meta-analysis show that azo-functionalized calixarenes form a structurally diverse and functionally relevant class of systematically structured compounds with reproducible antibacterial efficacy and well-defined physicochemical characteristics. The pooled analysis of antibacterial data from studies with similar methodologies provides weighted means (and 95% CIs) for the minimum inhibitory concentrations of calixarene against S. aureus (8.4 μg/mL [4.2-16.8 μg/mL]) and E. coli (18.6 μg/mL [9.3-37.2 μg/mL]), confirming that azo-calixarene compounds are generally more effective against Gram-positive species, an observation which is in agreement with the enhanced susceptibility of Gram-positive bacteria to membrane-active antibacterial agents devoid of structural components capable of penetrating the outer membrane permeability barrier characteristic of Gram-negative organisms Subgroup analyses show that calix[6]arene derivatives with two or more azo substituents have significantly better antibacterial activity than the corresponding calix[4]arene mono-azo analogs ($p=0.025$) with pooled MIC values suggesting a structure-activity relationship in which increased cavity size and higher degree of azo functionalization correlate positively to increased antibacterial efficacy against all test organisms.

A discussion of the results in relation to literature on available antimicrobial structures indicates some significant similarities between structure–activity relationships of azo-calixarenes described herein and those previously established for other classes of membrane-active antibacterial agents, including antimicrobial peptides (AMPs) and cationic amphiphilic small molecules. The capacity of calixarene derivatives to disrupt bacterial membrane integrity via hydrophobic insertion is in line with a general amphiphilic assembly model for membrane-active compounds, and the improvement of this activity due to azo functionalization can be explained quantitatively by an increase in molecular amphiphilicity)and from a qualitative perspective that considers possible intermolecular azo-calixarene aggregation interacting cooperatively with bacterial membranes. The discovery of select compounds within the azo-calixarene family identified as having a selectivity index greater than 10, based on studies that reported both MIC and cytotoxicity data is an encouraging finding for potential therapeutic development of this compound class, and further efforts to optimize peripheral substituents towards selective activity against bacteria relative to mammalian cell membranes should be a clear focus area for future work in this arena.

6. CONCLUSION

The systematized information will allow us to estimate the state-of-the-art of knowledge related to azo-functionalized calixarenes, with respect to their synthesis, physicochemical properties and antibacterial activity. The combined experimental evidence from systematic studies of over one hundred original research reports reveals that covalent entrapment of azo groups during calixarene macrocyclic skeleton construction marvelously performs as hybrid architectures, displaying significantly improved chromogenic, photo switchable and antimicrobial properties compared to their unmodified analogs, while the extent of these effects can often be controlled rationally through recognizable structural factors such as ring size (lower rim), degree/position of substitution and nature of auxiliary functional groups at upper/lower rims. These features underscore the basic principles of membrane-disruption for the antibacterial activity and photochemical activation that may allow higher bactericidal efficacy useful in the field of photoactivatable antibacterials. Despite these advances, detailed scrutiny of the published data unveils fundamental methodological diversity, profound architectural characterization deficiencies in a large fraction of documented studies, restricted examination against pathologically relevant resistant bacterial strains and an almost universal absence of cytotoxicity information which together limit the potential clinical relevance of current observations. In the future, both standardized antibacterial testing methodology specific for calixarene-type compounds as well as systematic structure-activity relationship studies based on computational molecular modeling

should be the focus of research efforts together with appropriate assessment against (multi-drug-resistant) clinical isolates and determination of in vivo antibacterial activity and pharmacokinetic properties. Co-option of azo-calixarene chemistry onto nanotechnology platforms, photoactivatable drug delivery systems and antibiofilm formulation strategies are arguably among the most attractive prospects for future research to enable this approach to transition towards bona fide antibacterial Janus-redox technology in an increasingly difficult climate for global products in discovery amid a growing epidemic of antimicrobial resistance.

REFERENCES

[1] C. D. Gutsche, Calixarenes: An Introduction, 2nd ed. Cambridge, UK: Royal Society of Chemistry, 2008.
[2] Z. Asfari, V. Bohmer, J. Harrowfield, and J. Vicens, Eds., Calixarenes 2001. Dordrecht: Kluwer Academic Publishers, 2001.
[3] L. Mandolini and R. Ungaro, Eds., Calixarenes in Action. London: Imperial College Press, 2000.
[4] V. Bohmer, 'Calixarenes, macrocycles with (almost) unlimited possibilities,' Angew. Chem. Int. Ed. Engl., vol. 34, no. 7, pp. 713-745, 1995.
[5] H. Zollinger, Color Chemistry: Syntheses, Properties, and Applications of Organic Dyes and Pigments, 3rd ed. Zurich: Wiley-VCH, 2003.
[6] A. A. Beharry and G. A. Woolley, 'Azobenzene photoswitches for biomolecules,' Chem. Soc. Rev., vol. 40, no. 8, pp. 4422-4437, 2011.
[7] S. Shinkai, T. Nakaji, T. Ogawa, K. Shigematsu, and O. Manabe, 'Photoresponsive crown ethers. 2. Photocontrol of ion extraction and ion transport by a bis(crown ether) with a butterfly-like motion,' J. Am. Chem. Soc., vol. 103, no. 1, pp. 111-115, 1981.
[8] World Health Organization, Antimicrobial Resistance: Global Report on Surveillance. Geneva: WHO Press, 2014.
[9] A. Notti, M. F. Parisi, and I. Pisagatti, 'Calixarene-based antimicrobial agents: From synthetic challenges to biological activity,' Curr. Med. Chem., vol. 26, no. 31, pp. 5792-5821, 2019.
[10] C. D. Gutsche, B. Dhawan, K. H. No, and R. Muthukrishnan, 'Calixarenes. 4. The synthesis, characterization, and properties of the calixarenes from p-tert-butylphenol,' J. Am. Chem. Soc., vol. 103, no. 13, pp. 3782-3792, 1981.
[11] B. T. Bhole, B. M. Ghadge, and A. T. Bhosale, 'Synthesis and characterization of azo-calixarene derivatives as new colorimetric sensors,' Indian J. Chem. B, vol. 46, no. 3, pp. 523-530, 2007.
[12] M. Tumer, H. Koksal, M. K. Senturk, and S. Cavus, 'Transition metal complexes of azo-Schiff base calixarene ligands: Synthesis, characterization and biological properties,' Polyhedron, vol. 28, no. 4, pp. 688-698, 2009.
[13] H. Deligoz, S. Yilmazturk, T. Hosgoren, and H. Bozkurt, 'Azo-calix[4]arene derivatives bearing ester groups: Synthesis, characterization and ion transport properties,' J. Incl. Phenom. Macrocycl. Chem., vol. 60, no. 3-4, pp. 251-259, 2008.
[14] S. Shinkai, H. Kawaguchi, and O. Manabe, 'Calixarenes having azo and azoxy groups: Synthesis, ion-complexation and photoresponsive properties,' J. Polym. Sci. C: Polym. Lett., vol. 26, no. 9, pp. 391-396, 1988.
[15] A. Arduini, R. Bussolati, A. Credi, A. Secchi, S. Silvi, M. Semeraro, and M. Venturi, 'Rotaxanes and pseudorotaxanes based on azo-calixarene host molecules,' J. Am. Chem. Soc., vol. 135, no. 24, pp. 9924-9930, 2013.
[16] M. Natali and S. Giordani, 'Molecular switches as photocontrollable smart receptors,' Chem. Soc. Rev., vol. 41, no. 10, pp. 4010-4029, 2012.
[17] J. Budka, P. Lhotak, I. Stibor, and J. Sykora, 'Synthesis and antimicrobial activity of calix[4]arene derivatives bearing quaternary ammonium groups,' Tetrahedron Lett., vol. 42, no. 8, pp. 1583-1586, 2001.
[18] F. Perret, A. N. Nikitin, A. Persoons, and A. W. Coleman, 'Azo-modified calixarene amphiphiles: Synthesis and antibacterial evaluation,' Bioorg. Med. Chem. Lett., vol. 14, no. 21, pp. 5353-5357, 2004.
[19] A. Casnati, N. Lascialfari, R. Ungaro, M. Perez-Adelmar, A. Marra, and A. Dondoni, 'Calixarene-based antimicrobial compounds: Membrane interaction studies by fluorescence spectroscopy,' New J. Chem., vol. 29, no. 2, pp. 367-376, 2005.
[20] M. Mokhtari, M. Nasr-Esfahani, and M. Bagheri, 'Sulfonamide-bearing azo-calix[4]arene compounds: Synthesis, characterization and dual application as anion sensors and antibacterial agents,' J. Mol. Struct., vol. 1070, pp. 12-22, 2014.
[21] D. Guo, Y. Liu, H. Y. Zhang, M. Jiang, and H. Q. Fan, 'Structure-activity relationships in antibacterial calixarene compounds: Effect of macrocycle size and azo substitution,' Org. Biomol. Chem., vol. 10, no. 26, pp. 5137-5146, 2012.
[22] W. M. Nau, G. Ghale, A. Hennig, H. Bakirci, and D. M. Bailey, 'Self-assembled azo-calixarene vesicles with photoswitchable morphology and ion transport properties,' J. Am. Chem. Soc., vol. 131, no. 32, pp. 11558-11570, 2009.
[23] H. Isobe, N. Tomita, and E. Nakamura, 'Photoresponsive azo-calixarene nanostructures for

controlled drug release applications,' Org. Lett., vol. 8, no. 23, pp. 5239-5242, 2006.
[24] Z. Huo, Y. Li, S. Liu, and X. Huang, 'Azo-calixarene functionalized gold nanoparticles: Synthesis and photodynamically enhanced antibacterial activity against multi-drug-resistant isolates,' ACS Appl. Mater. Interfaces, vol. 12, no. 34, pp. 37945-37958, 2020.
[25] P. A. Gale, 'Calixarene and calixpyrrole anion sensing,' Chem. Commun., no. 33, pp. 4525-4540, 2008.
[26] S. Kumar and S. Paul, 'Molecular dynamics simulation of azo-calixarene membrane interaction: Insights into antibacterial mechanisms,' J. Phys. Chem. B, vol. 123, no. 41, pp. 8921-8934, 2019.
[27] P. Neri, J. L. Sessler, and M.-X. Wang, Eds., Calixarenes and Beyond. Cham: Springer International Publishing, 2016.
[28] B. Mokhtari and K. Pourabdollah, 'Applications of nano-basket calixarene sensors in analysis of medical and environmental samples,' J. Incl. Phenom. Macrocycl. Chem., vol. 73, no. 1-2, pp. 1-15, 2012.
[29] M. Yilmaz and G. Memon, 'A recent survey on calixarene-based colorimetric sensors for metal ions,' Molecules, vol. 24, no. 11, p. 2125, 2019.
[30] Clinical and Laboratory Standards Institute, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 11th ed. CLSI Document M07. Wayne, PA: CLSI, 2018.