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**MINI-REVIEW ARTICLE**

# Cyclotriphosphazene-based Derivatives for Antibacterial Applications: An Update on Recent Advances

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**Abstract:** As a phosphorus scaffold, hexachlorocyclotriphosphazene (HCCP) is widely used for the synthesis of varieties of derivatives, including metal-binding complexes and several unique organometallic compounds, which exhibit potential catalytic, flame retardant and biological activities. Some metal-binding HCCP derivatives have shown antibacterial activities as free ligands and metal complexes. These derivatives can also serve as building blocks for the formation of antibacterial metal-containing polymers. This mini-review is focused on the design and development of HCCP derivatives as potential antibacterial agents with representative examples as well as antibacterial mechanisms from recent years.

**Le Wang**

**Keywords:** Hexachlorocyclotriphosphazene(HCCP), antibacterial, antibacterial mechanism, metal, ligand, polymer.

## 1. INTRODUCTION

Bacterial infections are considered serious public health concerns by several international organizations and local agencies, as they may lead to high mortality [1-3] and have been well illustrated by the few pandemic plagues in history. Infections by some common Gram-positive pathogenic bacteria (*e.g*., *Staphylococcus*, *Streptococcus*, and *Enterococci*) are still the main causes of human morbidity and death worldwide [4, 5], especially those antibiotic resistant ones such as MRSA (methicillin-resistant *Staphylococcus*) and VRE (vancomycin-resistant *Enterococci*), although some less common ones can also cause serious illness such as tetanus-causing *Clostridium difficile*; whereas the widely distributed Gram-negative bacteria can be opportunistic such as *Pseudomonas aeruginosa*, pathogenic such as the plague-causing *Yersinia pestis*, or even life-supporting ones such as certain types of the very common guts bacterium *Escherichia coli*. The emergence of antibiotics revolutionized modern medicine, which has been commonly used for the prevention and treatment of bacterial infections, including the disastrous plague. However, continuous extensive use of antibiotics, and especially their misuse, has resulted in bacterial resistance [6, 7] and increased the number of multiple-drug resistant bacteria worldwide, namely MRSA and VRE. The lack of effective last-resort treatment of infections results in high mortality [8, 9]. Based on this fact, the World Health Organization (WHO) claims that it is a priority to develop novel antibacterial drugs for the treatment of multidrug-resistant infections [10].

In addition to further discover new antibiotics, natural strategies have also been developed for combatting infectious microorganisms, including the use of phages, antimicrobial peptides, bacteriocins, probiotics, fecal transplants, predatory bacteria, antibodies, and therapeutics produced with biotechnology (such as the use of genetically modified bacteriophages, lysins, and the CRISPR-Cas9 system) [11-13]. However, synthetic approaches are still preferable for potential production of effective bactericides that are immune tolerable and relatively less expensive [14]. Moreover, synthetic analogs can mimic natural antibiotic actions with potentially improved antibacterial efficacy, and can possibly afford new antibiotic molecules against drug-resistant bacteria. Since bacteria can form biofilms which render those bacteria relatively more resistant to bactericides [15, 16], the development of coating materials resistant to microbial adhesion, capable of killing bacteria, and/or as matrices for controlled release of antibacterial drugs has also been an area of intense research.

Hexachlorocyclotriphosphazene ($N_3P_3Cl_6$, HCCP) is a well-known phosphorus-containing cyclic compound that contains six reactive P-Cl bonds (Fig. **1**). Since its first synthesis in the 19th century(1834s), cyclotriphosphazene has been an essential phosphorus scaffold in phosphorus chemistry for the synthesis of a great variety of derivatives [17-19]. As its chemical and physical properties are influenced by the connected substituents [20], many HCCP derivatives with specific substituents have been prepared for broad applications, such as the use as flame retardant additives [21-23], fluorescent materials [24, 25], and liquid crystals [26]. Recently, their use in biomedical fields has attracted particular attention, for instance, as anti-HIV, anticancer, and anti-neurodegenerative agents [27-30]. In this review, we highlight the latest antibacterial research and future perspectives of HCCP-based derivatives and their complexes and composite materials, as well as their use as drug delivery systems.

## 2. HCCP-BASED DERIVATIVES FOR ANTIBACTERIAL APPLICATIONS

With six chemically active chlorine atoms, the cyclotriphosphazene core can undergo substitution reactions to yield various derivatives [31, 32]. The synthesis of HCCP-based antibacterial derivatives is mainly focused on nucleophilic substitution reactions

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with antibacterial active moieties, such as alkoxy, phenoxy, thiol, and amido groups. In this review, two preparation methods are described: a) direct linking of active groups to HCCP to form novel antibacterial molecules or ligands for complexation with metal ions and b) the utilization of HCCP as a core to form polymers and antibacterial composites. These general methods are illustrated in Fig. **(1)** whereas Table **1** summarizes relevant information regarding the examples presented in the review, namely the type of HCCP derivatives, the synthetic approaches used in the preparations, the bacterial strains that are sensitive to the compounds, and the Minimum Inhibitory Concentration (MIC) of the compounds.

Although cyclotriphosphazene itself is an active antimicrobial agent due to the bactericidal effect of the phosphazene group [33], the modification of the cyclotriphosphazene core can be considered a significant strategy to synthesize novel antibacterial drugs. This section is thus organized into three parts: 1) cyclotriphosphazene-based derivatives with antibacterial activity; 2) metal complexes of cyclotriphosphazene-based derivatives with antibacterial activity; and 3) polymeric cyclotriphosphazene-based derivatives as antibacterial agents or as carriers for antibacterial drugs.

### 2.1. Cyclotriphosphazene-based Derivatives with Antibacterial Activities

As the Schiff base imine group (C=N) may promote antibacterial activity [34-36], its oxime derivatives (C=N–OR) have been introduced into HCCP-based systems and their biological action investigated. A series of oxime-phosphazene derivatives were reported (**1a-j**, Fig. **2**), and their antibacterial and antifungal properties verified with the agar-well diffusion method [37] to exhibit

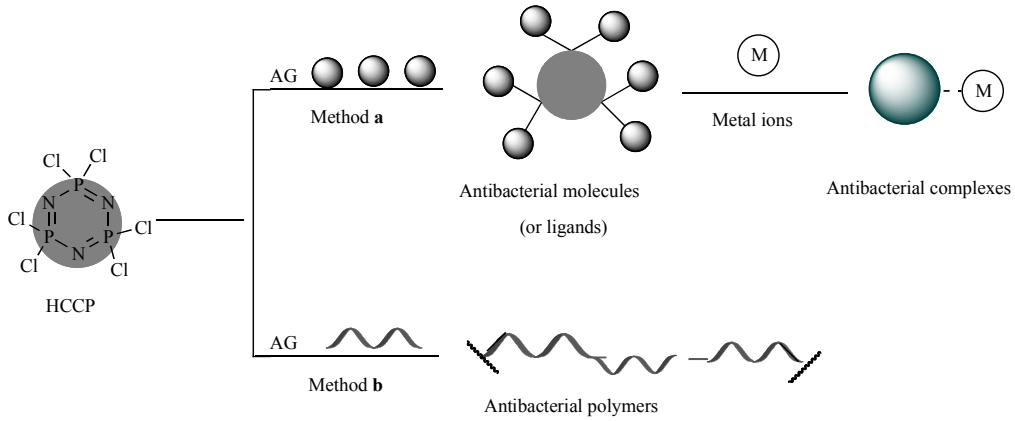



**Fig. (1).** Schematic procedures for the preparation of HCCP-based antibacterial derivatives. Method **a**: direct linking of AG (active groups) to form novel antibacterial molecules or ligands for metal binding; Method **b**: utilization of HCCP as a core to link macromolecules to form antibacterial polymers.

**Table 1. Summary of HCCP-based derivatives and their antibacterial applications, as well as the reaction approaches.**

| Systems and approaches | HCCP-based derivatives | Bacterial strains | MIC (μg/mL) | Refs. |
|---|---|---|---|---|
| antibacterial HCCP-based derivatives by method **a** | oxime-phosphazenes | *S. aureus; E. faecalis; E. coli; K. pneumonia; A. niger; C. albicans* | 100–25 | [37] |
| | aromatic ring-linked imine phosphazenes | *S. aureus; E. coli; P. aeruginosa; K. pneumonia* | 240–0.94 | [38] |
| | phenol-linked imine phosphazene | *B. subtilis; P. aeruginosa* | Nd [a] | [40] |
| | naphthalimide-BODIPY-phosphazenes | *S. aureus* | Nd [a] | [47] |
| | spirocyclotriphosphazenes | *B. Subtilis; C. tropicalis and C. albicans* | 416–5.97 [b] | [52] |
| | spiro-bino-spiro cyclotriphosphazene | *B. Cereus; B. subtilis; E. faecalis; P. vulgaris* | Nd [a] | [54] |
| | fluorenylidene-bridged phosphazenes | *S. aureus; E. coli; P. aeruginosa* | Nd [a] | [55] |
| HCCP-based complexes by method **a** | Cr(III)/Fe(III)/Cu(II)/Mn(II) complex | *S. aureus; E. coli; P. aeruginosa* | Nd [a] | [61] |
| | ferrocenyl bisspirophosphazene | *B. Cereus; M. tuberculosis H37Rv* | Nd [a] | [64] |
| | dispirocyclic ferrocene phosphazene | *Vulgaris; K. pneumoniae; E. coli* | Nd [a] | [65] |
| | Ru(II) complex | *S. aureus; E. coli; K. pneumoniae; C. albicans; R. rubra* | Nd [a] | [68] |
| | silver(I) metallophosphazene complexes | *S. aureus; E. coli; P. aeruginosa; M. tuberculosis H37Rv M. bovis BCG Pasteur* | 0.20–39 [b] | [74] |
| HCCP-based derivatives as antibacterial polymers by method **b** | polymer CP/BZ/Bmi composite | *S. aureus; E. coli* | Nd [a] | [82] |
| | polymer ATCP/$FTiO_2$/Bc-Ze composite | *S. aureus; E. coli* | Nd [a] | [84] |
| | polymer POSS/PZI composite | *S. aureus; E. coli* | Nd [a] | [87] |
| | polymer PEI/HCCP composite | *aureus; E. coli* | Nd [a] | [90] |
| | AMX-loaded polyphosphazene | *S. aureus; B. subtilis* | Nd [a] | [97] |
| | CPFX(NFX)-loaded polyphosphazene | *E. coli* | 0.45 (0.58) | [105] |

[a]Not determined; [b]MICs were transformed by us from micromolars to micrograms per milliliter.

various antibacterial activities (MIC = 100~25 μg/mL) against two Gram-positive bacteria (*S. aureus* and *E. faecalis* ) and two gram-negative bacteria (*E. coli* and *K. pneumonia*). Among them, compounds **1g, 1h, 1j** with benzoyl, and **1i** with thiophene have a positive effect on these four bacterial pathogens and showed inhibitory zones of 23–30 mm with MIC=25 μg/mL. Compounds **1d-f** with a carbonyl group have only moderate activities against these four microorganisms with inhibitory zones of 17–21 mm and MIC of 50 μg/mL. Although the authors have not further discussed the antibacterial mechanism of the oxime phosphazene derivatives, it may be suspected that the imine group in the compound promotes antibacterial activity as previously observed. In addition, the results showed that aromatic rings such as benzoyl (**1g, 1h, 1j**) and thiophene(**1i**) show higher antibacterial activities than other substituents on the oxime moieties. This implies that the introduction of benzoyl or thiophene ring on the oxime phosphazene backbone can significantly improve the antimicrobial activity of the compounds. These results provide new strategies for the preparation of cyclotriphosphazene-based derivatives bearing antimicrobial activity.

Similarly, some other aromatic ring-linked imine phosphazene derivatives were prepared and investigated [38]. A series of aromatic ring-linked imine phosphazene derivatives were synthesized (**2a-j**, Fig. **3**), and their antibacterial was screened. These compounds show mild to good antibacterial activities (MIC=240–0.94 μg/mL) against either of the two Gram-positive/negative bacteria. Among compounds **2a-j**, **2b** with a chlorophenol group shows an excellent antimicrobial activity toward the Gram-positive *S. aureus* and Gram-negative *P. aeruginosa* and *E. coli* with MIC in the range of 3.75–0.94 μg/mL, better than the standard antibacterial drugs ciprofloxacin and gatifloxacin with MIC values of 15–1.875 μg/mL. Moreover, compound **2d** with only the phenol group exhibits a favorable activity against the Gram-negative bacteria *E. coli* ATCC 25922 with a MIC of 15 μg/mL and an acceptable antibacterial activity against *K. pneumoniae* CIP 53153 with MIC=30 μg/mL. The CN- and CO-containing **2j** shows promising antimicrobial activity against the Gram-positive bacterium *S. aureus* ATCC 25923 and the Gram-negative bacteria *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 with a MIC about 15 μg/mL. It seems that the aromatic ring-linked imine phosphazene derivatives that contain OH, Cl, and/or CN groups can promote antibacterial activity. These aromatic ring-linked imine derivatives were suspected to disrupt the cell wall, change the permeability of the plasma membrane, and affect protein synthesis of the microbes, causing bacterial death [39].

Recently, Lakshmikandhan *et al*. [40] prepared a phenol-linked imine phosphazene derivative (compound **3**) (Fig. **4**) aimed to use as an antibacterial additive. Compound **3** was added to epoxy nanocomposites with various weight percentages (1 wt%, 3 wt%, 5 wt%, and 7 wt%) to determine the optimal antibacterial activity. The results showed that the reinforced epoxy nanocomposite could im-

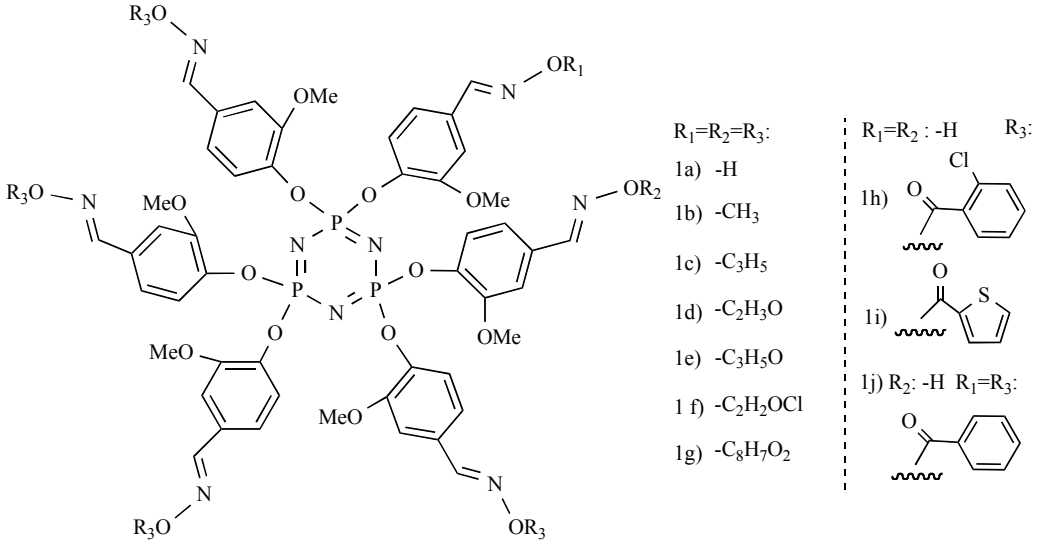



**Fig. (2).** Chemical structure of oxime phosphazene derivatives with antibacterial activities (compounds **1a-k**). Adapted from reference [37].

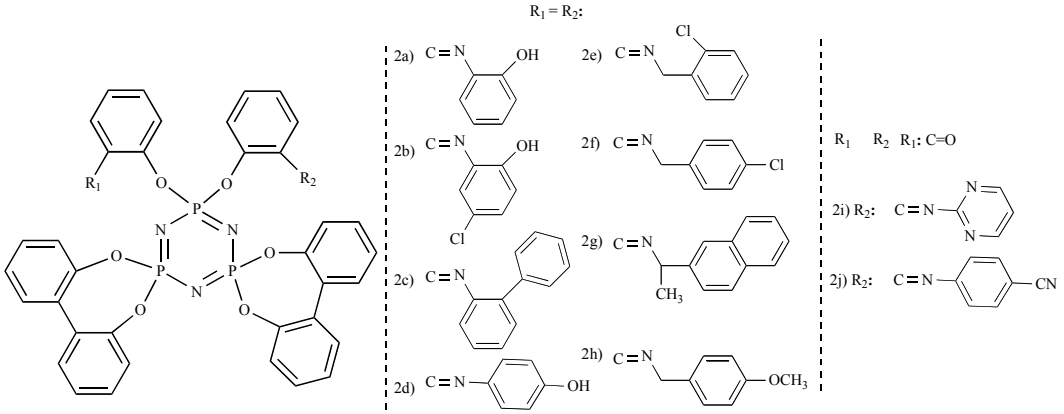



**Fig. (3).** Chemical structures of aromatic ring-linked imine phosphazene derivatives (compounds **2a-j**). Adapted from reference [38].

prove antimicrobial activity against the growth of *B. subtilis* and *P. aeruginosa*. The antimicrobial activity of the epoxy nanocomposites was enhanced with increasing amounts of **3** and reached the highest antibacterial activity at 7 wt%, showing inhibition zones for these two bacteria of 18 and 17 mm, respectively. However, whether or not the antibacterial activity of the nanocomposite is further enhanced with higher amounts of **3** was not conducted and could not be determined. The enhanced antibacterial activity of phenol-linked imine phosphazene/epoxy nanocomposites is presumably related to the lipophilicity of the nanocomposites. The delocalization of p-electrons increases the lipophilicity of the composites, which in turn promotes the decomposition of the bacterial cell wall, resulting in bacterial death. Furthermore, compound **3** can interfere with the permeability of cells, causing the outflow of electrolytes, nutrients, proteins, and genetic material, leading to cell death [41-43].

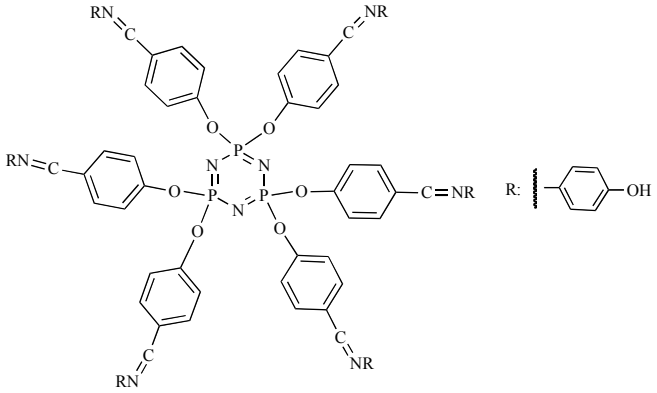


**Fig. (4).** Chemical structure of an imine-phosphazene derivative (compound **3**). Adapted from reference [40].

Some fluorophores with excellent photophysical properties(such as BODIPY and naphthalimide), can also be introduced into the HCCP-derived system and used for antibacterial applications. Some studies have pointed out that BODIPY can kill bacteria by producing singlet oxygen, which can initiate a non-specific killing of bacteria, without inducing resistance [44, 45]. Naphthalimide, a cyclic imide with a strong hydrophobicity and a large p-conjugated skeleton, shows antibacterial activities by interacting with target molecules in bacteria (*e.g*., DNA) through non-covalent forces (such as p-p stacking) [46]. Based on these research results, a cyclotriphosphazene cored naphthalimide-BODIPY dendrimeric system was developed (Fig. **5**) for antibacterial research [47]. The antibacterial activities of mono- and di-styryl-BODIPY substituted cyclotriphosphazene derivatives (compounds **4a,b**) against Gram-positive *S. aureus* and Gram-negative *E. coli* were tested by the use of the Kirby-Bauer disk diffusion method, showing inhibition zones of 16 to 23 mm against S. aureus respectively, but without significant effect on E. *coli* (at a concentration of $10^5$ CFU/mL). These findings suggest that the naphthalimide-BODIPY derivatives of cyclotriphosphazene may be more selective against Gram-positive bacteria and can have specific antibacterial applications.

The authors stated that the good antibacterial activity of derivatives **4** could be attributed to the presence of the BODIPY moieties. The BODIPY moieties have a photo-sterilization effect that can produce singlet oxygen to kill bacteria [45, 48]. Moreover, the interaction between the BODIPY moieties in the phosphazene derivative and the cell wall increases permeability of bacterial cells, which can also enhance their bactericidal activities [44]. The authors believe that the bactericidal effects of BODIPY can overcome the resistance of a variety of bacteria and that the naphthalimide-BODIPY-cyclotriphosphazene compounds can be successfully applied to defeat them if they are proven safe at clinical doses and demonstrated specific *in vivo*. Regardless, this design strategy for killing bacteria, which uses photosensitizers for the generation of singlet oxygen, is a potential direction for producing promising novel antibiotic agents.

The spirocyclic phosphazenes have attracted much attention for antibacterial applications, where the chiral cyclotriphosphazenes possess stereoisomeric properties [49]. Therein, bifunctional nucleophilic aromatic diamines are introduced into the HCCP-based system to produce spiro-cyclotriphosphazene derivatives [50, 51]. Akbas *et al*. [52] firstly introduced N-alkylmono (4-fluorobenzyl) diamine into the HCCP-based system to produce spirophosphazene, aiming to develop antimicrobial drugs against certain bacteria and fungi. This newly synthesized spirophosphazene was fully substituted by pyrrolidino or piperidino to form tetrapyrrolidino **5a-c** or tetrapiperidino **6a-c** phosphazene derivatives (Fig. **6**). The antibacterial and antifungal activities of these compounds assessed by the use of the agar well diffusion method showed an inhibition zone of 11 to 20 mm toward the Gram-positive *B. subtilis* and the fungi *Candida tropicalis* and *Candida albicans* at 2500 μM with MIC values ranging from 625 to 9.8 μM.

Among all compounds, compounds **5a-c** had good activity against *B. subtilis*, with the inhibition zone ranging from 11 to 16 mm. While compounds **6a-c** exhibited strong antifungal properties against *C. tropicalis* and *C. albicans*, and **6c** was the strongest antifungal compound against these two strains(inhibition zone: 20–18 mm *versus* 17–13 mm for **6a** and 17–12 mm for **6b**). The results indicated that this antimicrobial activity might be dependent on the chain length of the alkane diamine precursor and substituents (pyrrolidinyl or piperidino groups) in compounds **5** and **6**, *i.e*., the longer the chain length of the diamine precursor, the better the liposolubility and the more obvious the antibacterial activity [53]. It seems that the size of the substituted heterocyclic might also have some influence on the selectivity of antibacterial pathogens. For example, compounds **5** had high antibacterial activities toward Gram-positive bacteria, whereas compounds **6** were active against fungi.

Similarly, a selection of spiro-bino-spiro cyclotriphosphazene derivatives has been prepared with octapyrrolidino, morpholine, and 1, 4-dioxy-hetero-8-azaspiro (DASD) for antimicrobial research [54]. The with antibacterial activities of the derivatives **7a-c** (Fig. **7**) were screened with the agar well diffusion method, showing different antibacterial activities against Gram-positive *B. cereus*, *B. subtilis,* and *E. faecalis* and Gram-negative *P. vulgaris* with inhibition zones of 10–26 mm at high concentration of 5 mM. Compound **7a** with octapyrrolidino had antibacterial activities against *B. cereus*, *B. subtilis*, and *P. vulgaris* with inhibition zone diameters of 22–26 mm. It is worth noting that these values are close to those of standard drugs such as ampicillin (inhibition zone diameters: 10–35 mm) and chloramphenicol (inhibition zone diameters: 23–31 mm) under the same conditions. We speculate that octapyrrolidino may facilitate the antimicrobial activity of compound **7a**.

Fluorenyl can be used as a protective group to form bridged(bino) phosphazene derivatives. A few fluorenylidene-bridged cyclophosphazenes **8a-c** (Fig. **8**) have been reported to possess antibacterial activity against some Gram-positive and Gram-negative bacteria [55]. The derivatives **8b** and **8c** exhibit good antibacterial activities against *S. aureus* ATCC25923, *E. coli*

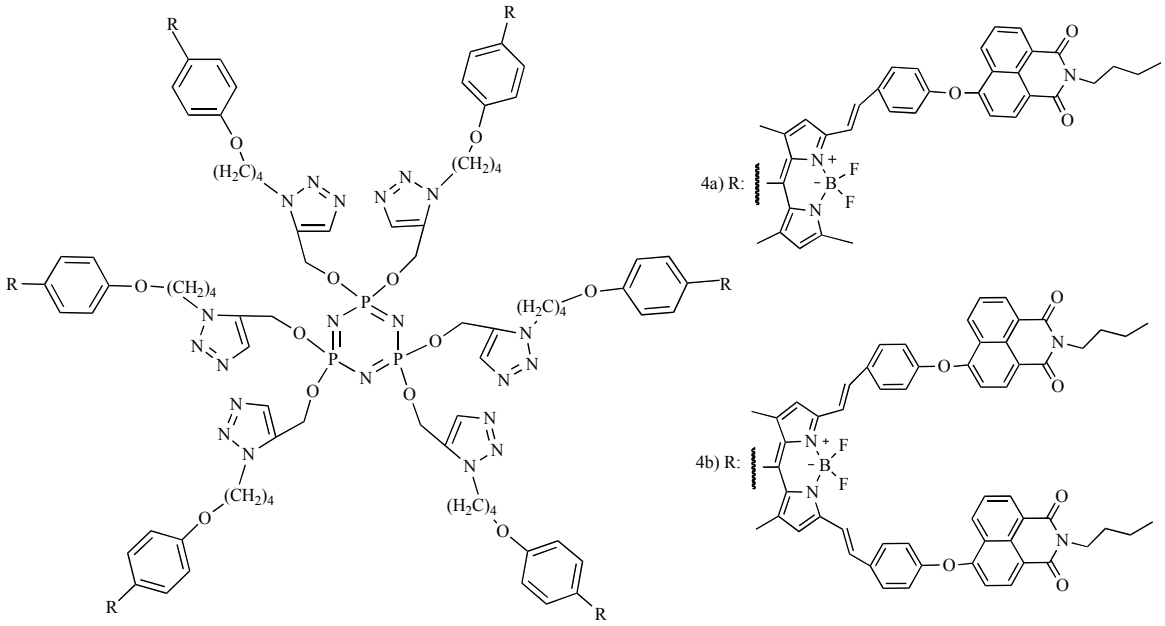



**Fig. (5).** The chemical structure of the naphthalimide-BODIPY-cyclotriphosphazene triads (compounds **4a, b**). Adapted from reference [47].

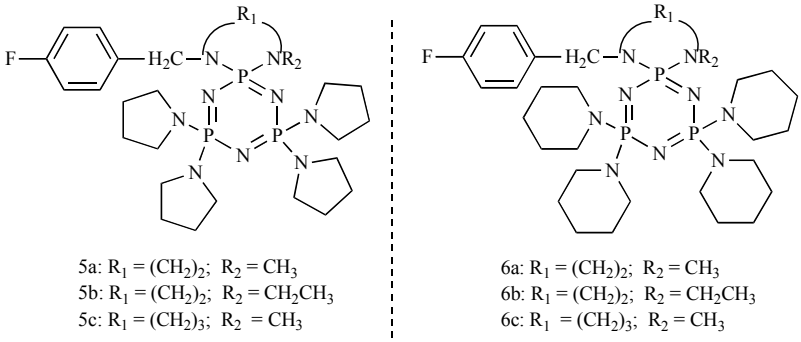



**Fig. (6).** The chemical structure of the tetrapyrrolidino spirocyclotriphosphazenes (compounds **5a-c**) and the tetrapiperidino spirocyclotriphosphazenes (compounds **6a-c**). Adapted from reference [52].

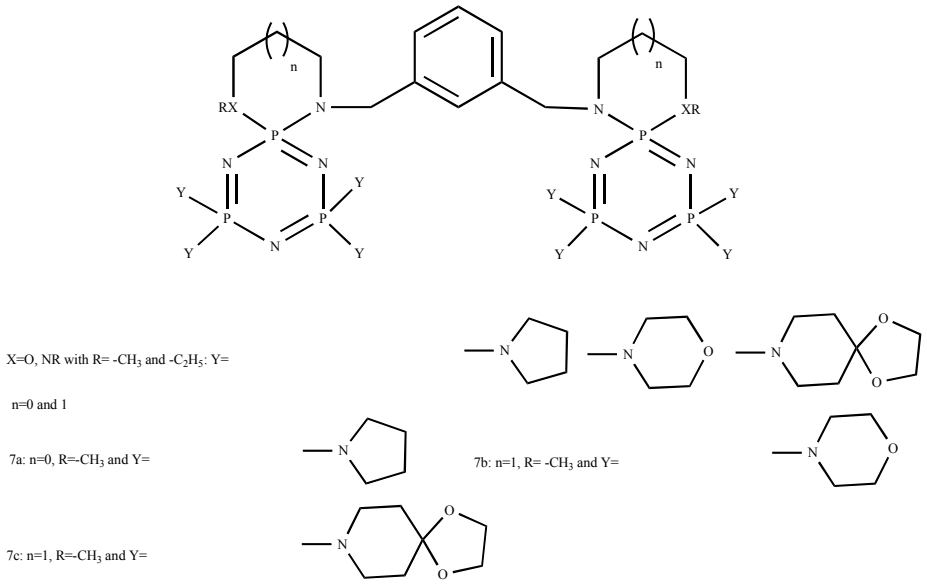



**Fig. (7).** The chemical structure of the spiro-bino-spiro cyclotriphosphazene derivatives **7** (general chemical structure) and compounds **7a-c**. Adapted from reference [54].

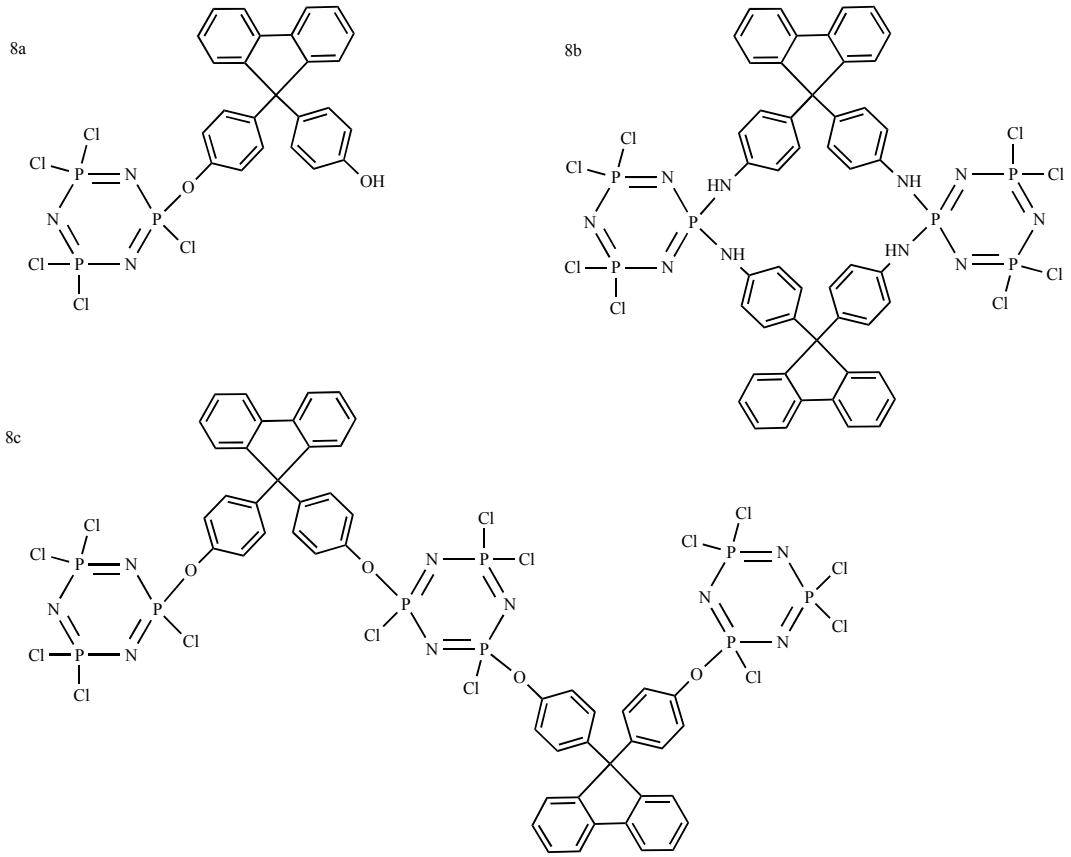



**Fig. (8).** Chemical structure of fluorenylidene-bridged cyclophosphazenes (compounds **8a-c**) with antibacterial activity. Adapted from reference [55].

ATCC35218, and *P. aeruginosa* ATCC27853 with inhibition zones ranging from 25 to 37 mm. The compound **8a** showed milder antibacterial activities against *S. aureus* ATCC25923 and *P. aeruginosa* ATCC27853 with inhibition zones of 10–35 mm. Specifically, the phosphonitrile derivatives (**8b** and **8c**) with two fluorene groups show better antibacterial activities than the phosphonitrile derivative **8a** with only one fluorene group. Thereby, we suspect that the presence of the fluorene group may favor the antibacterial effect. However, fluorenylidene-based antimicrobial agents are rarely reported in the literature, the mechanism of the antimicrobial activity of these derivatives still needs further investigation and confirmation.

### 2.2. Antibacterial Metal Complexes of Cyclotriphosphazene-based Ligands

Many organometallic macromolecules have shown significant activities against diverse cellular forms, including cancer/tumor cells, bacteria, and fungi, through various mechanisms such as their binding to nucleic acids and other biomolecules [56-60]. In this section, the chemistry and activities of a series of metal-binding HCCP-based derivatives and their metal complexes are discussed.

Owing to their high Lewis basicity, nitrogen- and oxygen-containing moieties have been introduced into HCCP-based system for the preparation of various metal-binding ligands. As shown in Fig. **(9)**, N, O-aminoethanol was linked to the HCCP cycle to form O-aminoethanol tetracyclochlorotrifluorophosphine (compound **9**) [61]. It was claimed that this ligand could complex with Cr(III), Fe(III), Cu(II) and Mn(II) transition metal ions, and that majority of the complexes displayed better antibacterial effect than the ligand. However, the structures of any of the complexes were not conclusively determined by means of structure-specific spectroscopic methods. The antimicrobial activity was evaluated based on the diffusion agar assay. The findings presented that the Fe(III) complex had significant activity on *P. aeruginosa*, which was superior to some known antibiotics such as metilmicine and gentamicin (inhibition zone diameter: ~17 mm versus ~14 mm for metilmicine and gentamicin). Furthermore, the antibacterial activity of Fe(III) complex against *P. aeruginosa* was comparable to the standard antibiotic amikacin (inhibition zone diameter: ~21 mm). It may be attributed to the interference of iron in the replication process of the genetic material occurring in microbes or disturbance of iron homeostasis [62], which needs to be further confirmed.

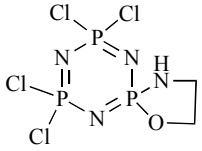


**Fig. (9).** The chemical structure of the ligand N, O-aminoethanol tetrachlorocyclotriphosphazene (compound **9**). Adapted from reference [61].

Furthermore, ferrocene is an essential organometallic compound with a very unique sandwich-like structure and diverse chemical reactivity. Along with other "metallocenes", ferrocene and derivatives have been investigated for their pharmaceutical properties, including anticancer, antibacterial, antifungal, and antimalarial activities [63]. A few ferrocenyl and tetrapyrrolidino-HCCP derivatives have been synthesized (**10**, Fig. **10**) and their antibacterial activities have been determined [64]. Results showed that compounds **10** had potential antimicrobial activity towards Gram-positive *B. cereus* and antituberculosis activity towards *M. tubercu-*

*losis H37Rv* (ATCC 27294). Compared with the HCCP-based core modified by the heterocyclic ring alone, these new compounds showed significantly better antibacterial activities, reflecting possible roles ferrocene plays. Whether it is due to the redox property of ferrocene or its possible specific interactions awaits future explorations.

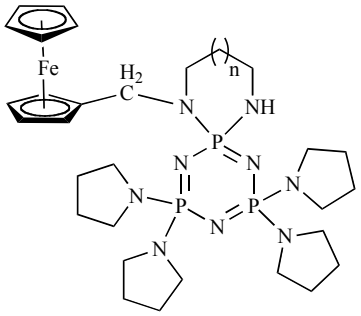


**Fig. (10).** The chemical structure of the ferrocenyl bisspirophosphazene derivatives **10** (n = 0, 1, 2). Adapted from reference [64].

The same research group further developed another ferrocene-containing phosphazene derivatives (**11** and **12**, Fig. **11)** [65]. These compounds showed varying degree antibacterial activities against bacterial strains with an inhibition zone of 8 to 18 mm at 2000 μM. It is shown that compound **12c** had the obvious antibacterial activity against *E. coli* ATCC35218(inhibition zone, ~14 mm), almost the same as that of the standard drug chloramphenicol (inhibition zone, ~8 mm). Along with studies of other metallocenes, the results herein suggest that ferrocene phosphazene derivatives may be potential antibacterial agents. To reveal the possible antibacterial mechanism of these compounds, the researchers also conducted DNA interaction studies, which can be a potential intracellular target. The results showed that compounds **11** and **12** can affect *in vivo* DNA synthesis, suggesting that ferrocenyl phosphazene derivatives can interact with genetic materials and hinder their replication [66, 67].

Phosphazene derivatives can also complex with Ru(II) ion for antibacterial applications, such as the one shown in Fig. **(12)** [68]. Their antibacterial and antifungal activities were screened with a disc diffusion and a dilution assay. The Ru(II) complex **13** showed stronger antibacterial activities against some Gram-positive and negative bacteria and yeast cultures than the free ligand. The antibacterial activities of the Ru(II) complex **13** were determined to be better than the standard drug gentamycin against *S. aureus* (MIC:~12.5 mg/mL versus 25 mg/mL for gentamycin), and achieving gentamycin against *E. coli* and *K. pneumonia* with MIC ~ 6.25 mg/mL. These antibacterial results suggest that these compounds deserve further investigation in view of their application as effective antibacterial agents.

The authors pointed out that the antibacterial activity of the Ru(II) complex **13** can be elucidated by the chelation theory of Tweedy [69]. The binding of the ligand with Ru(II) may reduce the polarity of the metal ion and enhance lipophilicity throughout the delocalization of pi electrons. Along with the lipophilic enhancement of the Ru(II) complex **13**, the complex may into the lipid membrane showing potential interactions with some biomolecules on microbial enzymes[70]. In addition, this group also claimed that these compounds may interfere with the cellular respiration/redox process, preventing protein synthesis, which limits further bacteria growth, which was attributed to a dependency on the properties of the bacteria membrane and the difference of ribosomes in microbial cells [71].

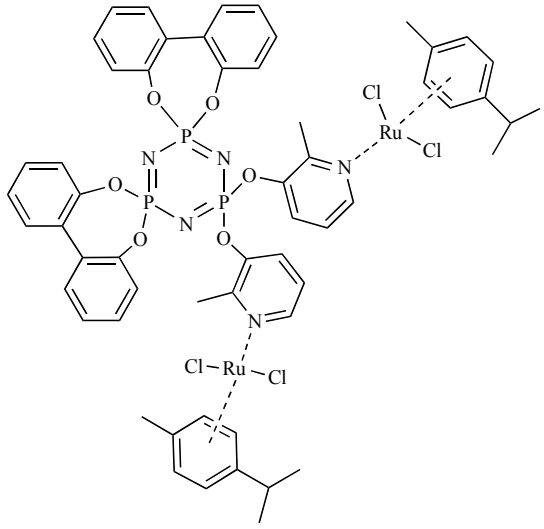


**Fig. (12).** The chemical structure of Ru(II) complex (compound **13**). Adapted from reference [68].

Silver in both atomic and ionic forms is widely used in antibacterial applications, showing strong inhibitory and bactericidal effects and are broad-spectrum antibacterial agents [72, 73]. Some derivatives of (amino)cyclophosphazenes were synthesized and several Ag(I) complexes of these derivatives were prepared and characterized with NMR and crystallography (**14a-i**; Fig. **13**) [74]. These Ag(I) complexes exhibit fantastic antibacterial activity against some Gram-positive and negative bacteria including *S.*

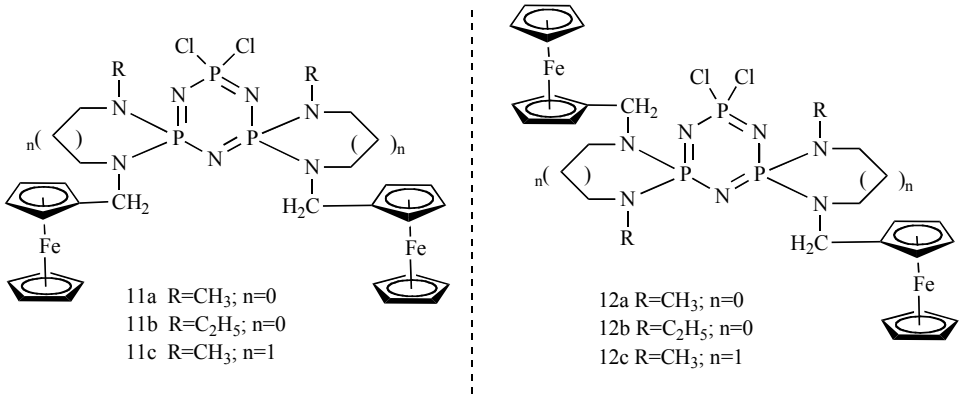



**Fig. (11).** The chemical structure of the dispirocyclic ferrocene phosphazene derivatives (compounds **11a-c** and **12a-c**). Adapted from reference [65].

*aureus*, *E. coli*, and *P. aeruginosa* and are also active against Mycobacteria strains (*M. tuberculosis* H37Rv and *M. Bovis* BCG Pasteur) with MIC values in a range of 0.12–15.6 μM. Their antibacterial activities are significantly better than that of $AgNO_3$ (MIC: ~31.25–15.6 μM), silver sulfadiazine (AgSD) (MIC: ~90–30 μM), and the phosphazene ligands (MIC: ~250–15.6 μM). The results showed most of the complexes were effective against *S. aureus* and *E. coli* with MIC among 7.8 and 0.12 μM. In particular, the complexes **13a**, **13b**, and **13f** exhibit the best antibacterial effect on *S. aureus* and *E. coli* with MIC values of 0.97–0.12 μM.

The broad-spectrum antibacterial activity of complexes **14** was suspected to be related to weak Ag-N bonds, which make the ligands easily replaced by sulfur or nitrogen donor sites of proteins and nucleotides in bacteria [75]. Alternatively, binding silver ions with mercapto groups in proteins [76] including membrane proteins can denature or inactivate those proteins and eventually cause bacteria death [77, 78]. Owing to their low toxicity and strong and broad-spectrum antibacterial activities, these Ag(I) metallophosphazenes complexes and analogues warrant further investigation.

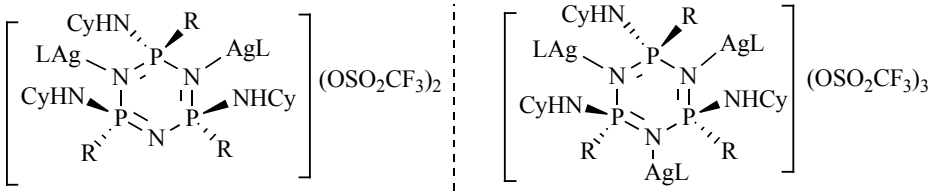
## 3. ANTIBACTERIAL CYCLOTRIPHOSPHAZENE-BASED POLYMERS

On account of their excellent antibacterial properties, such as relatively long antibacterial action, diverse antibacterial polymers have attracted much attention [79-81]. Cyclotriphosphazene-based polymers, for example, may possess antibacterial properties per se or may be used as carriers for antibacterial drugs, and have thus been previously evaluated and highlighted herein.

### 3.1. Cyclotriphosphazene-based Polymers with Antibacterial Properties

A polymer composite of cyclophosphazene(CP) with blended benzoxazine(Bz) and bismaleimide(Bmi) has been synthesized (Cp-Bz-Bmi **15**, Fig. **14**) and its applicability as an antibacterial agent investigated [82]. Different compositions of cyclophosphazene (5 wt%, 10 wt%, and 15 wt%) in the Bz-bmi copolymer exhibit higher antibacterial activities than pure Bz-bmi copolymer. As the weight percentage of cyclophosphazene increases, the inhibitory effect on bacteria becomes more pronounced. The Cp(15wt%)-Bz-Bmi composite restrains the growth of *S. aureus* and *E. coli*, showing 11 and 10 mm in inhibition diameter, respectively. The antibacterial mechanism of **15** seems to be related to the amount of cyclotriphosphazene present in the composite, and the authors stated that the van der Waals linked with the polymer and the bacteria [83]. However, this proposal needs to be further investigated clearly for their potential use as antibacterial coating materials.

A covalent composite of aminophenol-cyclophosphazene (ATCP) and functionalized $TiO_2$ nanoparticles ($FTiO_2$) with benzoxazine (Bz) cyanate ester (CE) was synthesized and evaluated as a coating material which shows anti-corrosion and antibacterial activities against *S. aureus* and *E. coli* (**16**, Fig. **15**) [84]. The weight percentages of ATCP (5, 10, and 15 wt%) and $FTiO_2$ nanoparticles (1, 3, and 5 wt%) were varied to reveal optimal antibacterial activities. The results showed that the 15 wt% ATCP-incorporated Bz-CE composite exhibits better antibacterial activity than the original Bz-CE polymer, and the composite ATCP(15%)/$FTiO_2$(5%)/Bz-CE showed considerable antibacterial




R=NHCy*, **14a**) L: $PPh_3$,**14b**) L: $PPh_2Me$

R= $NMe_2$, **14c**) L: $PPh_3$,**14d**) L: $PPh_2Me$

R=NHCy*, **14e**) L: $PPh_3$, **14f**) L: $PPh_2Me$, **14g**) L: 1,3,5-triaza-7-phosphaadamantane

R=$NMe_2$, **14h**) L: $PPh_3$, **14i**) L: $PPh_2Me$

* Cy = Cysteine

**Fig. (13).** The chemical structures of two series of silver(I) metallophosphazenes (**14a-i**). Adapted from reference [74].

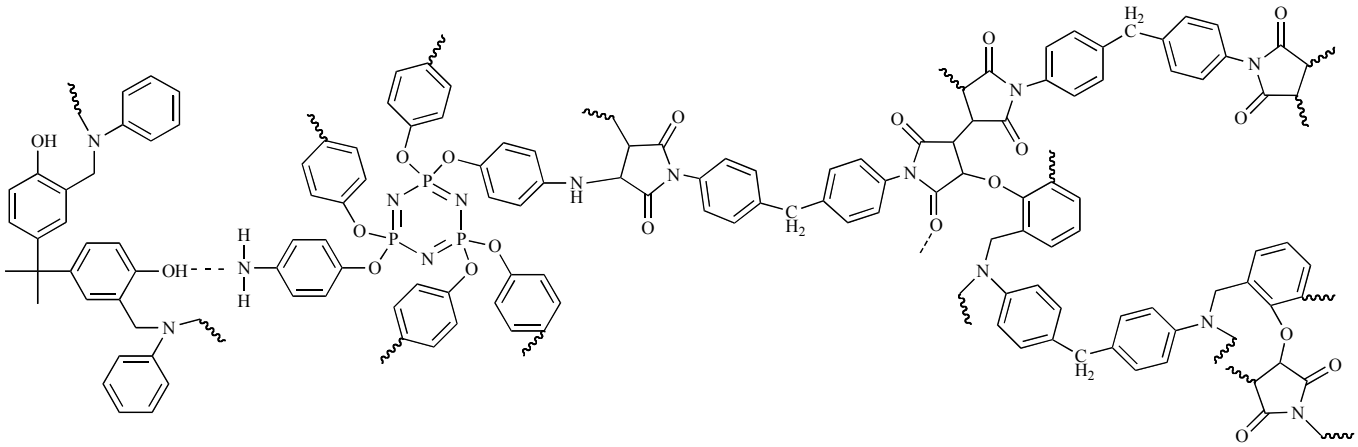


**Fig. (14).** Chemical structure of cyclophosphazene (Cp) blended with benzoxazine (Bz) and bismaleimide (Bmi) polymer composite (Cp-Bz-Bmi, **15**). Adapted from reference [82].

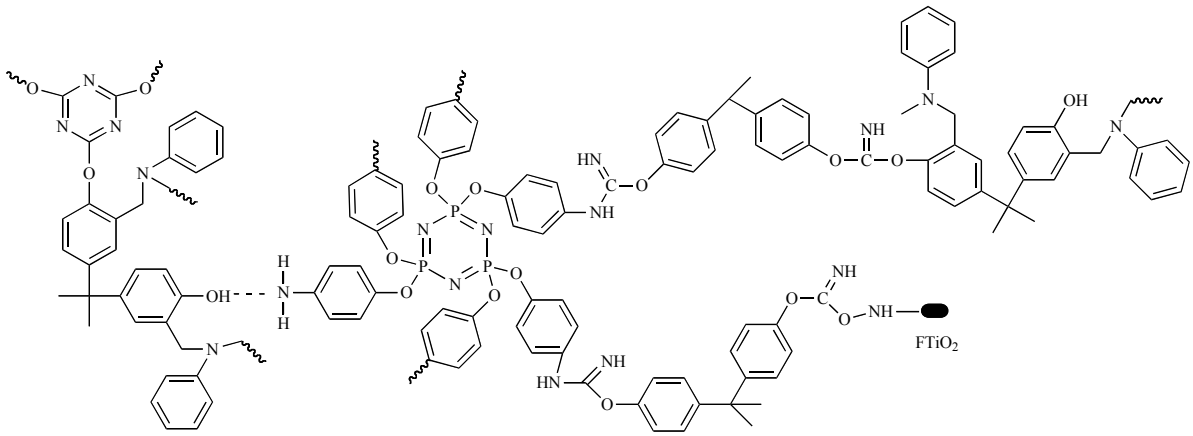



**Fig. (15).** Chemical structure of the covalent composite of aminophenol-cyclophosphazene (ATCP) and functionalized $TiO_2$ nanoparticles ($FTiO_2$) with benzoxazine (Bz) cyanate ester (CE) polymer (**16**). Adapted from reference [84].

properties against *S. aureus* and *E. coli* with suppression zones of 21 and 20 mm, respectively. The unique photocatalytic activity of the $FTiO_2$ nanoparticles may also contribute to the antibacterial effect as reported elsewhere [85]. Since UV-irradiated $TiO_2$ nanoparticles can produce the powerful oxidation agent singlet oxygen, which can degrade most organic compounds in bacterial cells [86], $TiO_2$ nanoparticles thus can be expected to contribute to the antibacterial effect of **16**. Thus, this material warrants further development for antibacterial applications in medical facilities.

A polyhedral oligomeric silsesquioxane (POSS)-crosslinked phosphazene polyimide (PZI) nanocomposites (POSS/PZI nanocomposites) was synthesized (17, Fig. **16**), and its antibacterial activities against S. aureus G(+) and E. coli G(-) investigated [87]. The antibacterial activity of 17 was detected to be better (with an inhibition zone in well diffusion assay of 13-15 mm) than that of the PZI matrix (11 mm). Nanocomposites of different concentrations of POSS in the PZI matrix (1, 5 and 10 wt% POSS/PZI) show antimicrobial activities against *E. coli* and *S. aureus* with the POSS(10wt%)/PZI nanocomposite exhibiting the best antimicrobial effect (15 and 14 mm, respectively). The results suggest that the silica constituent POSS may be the key factor in this antibacterial nanocomposite [88]. It is also probable that silica nanoparticles increase the contact area between the composite and the bacteria, rendering a higher interaction with the PZI matrix, which improves antibacterial efficiency [89].

A cyclotriphosphazene-containing antibacterial polymer based on positively charged polyethyleneimine (PEI/HCCP) has recently been synthesized (**18**, Fig. **17**) to serve as an antibacterial coating

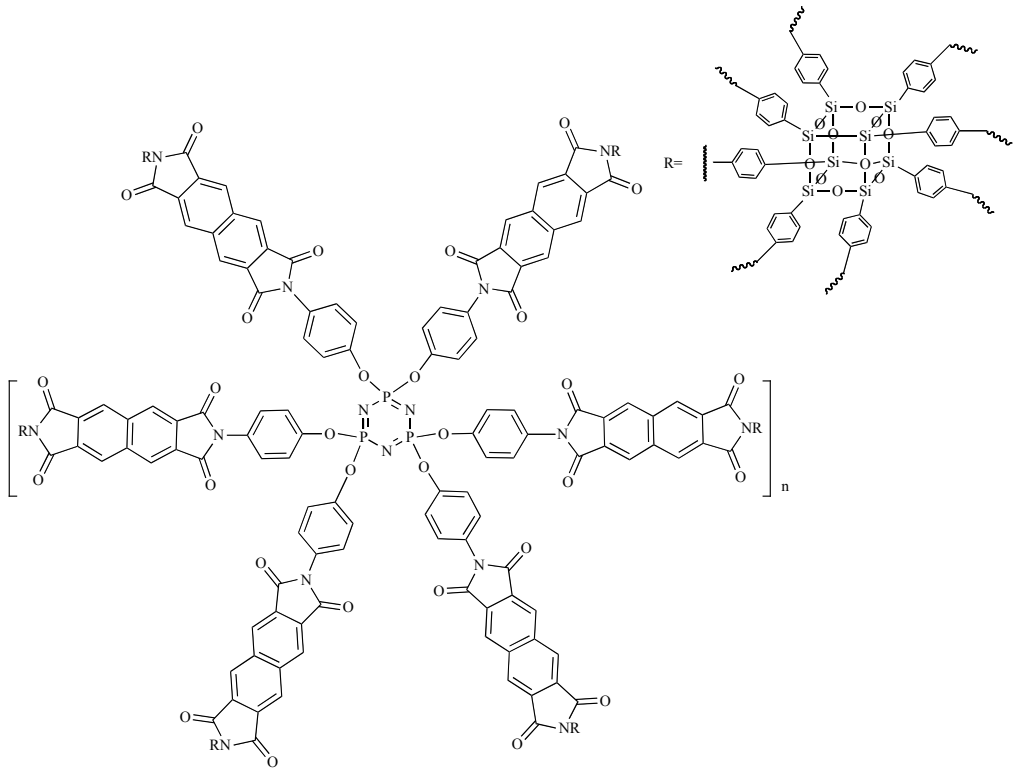



**Fig. (16).** Chemical structure of polyhedral oligomeric silsesquioxane (POSS)-crosslinked phosphazene polyimide (PZI) nanocomposites (**17**). Adapted from reference [87].

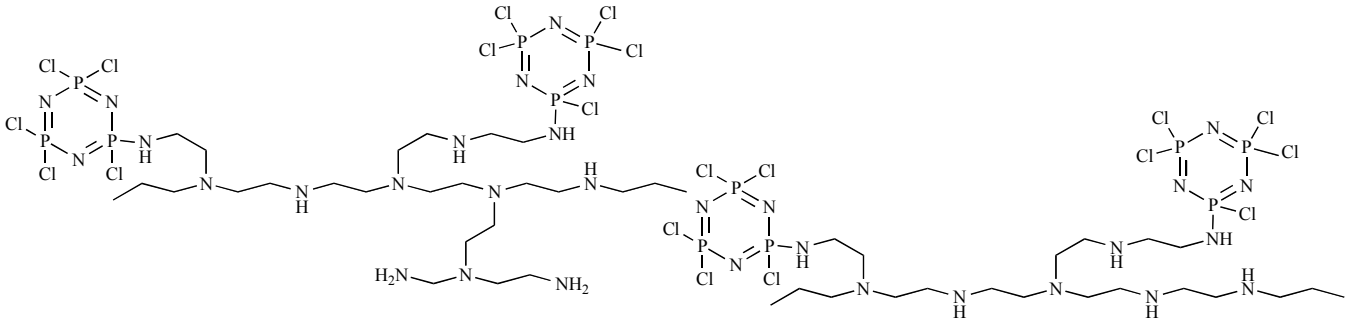


**Fig. (17).** Chemical structure of polyethyleneimine/hexachlorocyclotriphosphazene (PEI/HCCP) polymer (**18**). Adapted from reference [90].

over a polysulfone substrate and for the preparation of nanofiltration membranes [90]. Its antibacterial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* was screened with colony-count method, showing nearly 100% bacterial inhibition rate against *S. aureus* and *E. coli* (at $10^7$ CFU/mL). Therein, the bacteria at $10^7$ CFU/mL were successfully killed in less than 20 minutes. The combination of PEI with HCCP clearly resulted in an obviously effective antibacterial material.

Owing to their polycationic structure, polyethyleneimines (PEI) are potent antibacterial moieties [91-93]. The antibacterial activities of **18** can be attributed to the cationic charges of PEI, which promotes bacteria attachment through electrostatic attraction and interferes with bacteria viability [94] and also to the presence of HCCP, which renders the polymer with higher hydrophobicity. The mechanisms for cationic moiety-caused bacteria death are not very well understood, but likely associated with cell wall and membrane disruption [60]. At the same time, the hydrophobic interaction of the HCCP moieties with bacteria may render the formation of bacterial biofilms more difficult and impact bacterial growth [95, 96].

### 3.2. Cyclotriphosphazene-based Polymers as Antibacterial Drug Carriers

Some specific cyclotriphosphazene derivatives can form hydrogels for the delivery of antibacterial drugs. As shown in Fig. **(18)**, a novel biodegradable hydrogel was synthesized by crosslinking formyl-phosphazene with chitosan *via* imine bond formation between the formyl group and the amino moiety (**19**) which can serve as a carrier for the widely used effective β-lactam antibiotic amoxicillin (AMX) as a model drug [97]. Through intermolecular forces (H-bonding and *van der Waals* forces), AMX can be loaded into and retained by this hydrogel **19**. The antibacterial activities of AMX-**19** against *S. aureus*, *B. subtilis*, and *E. coli* were determined with the disk diffusion method, showing positive antibacterial effects on *S. aureus* and *B. subtilis* G(+), yet not against *E. coli* G(-) which is consistent with *E. coli* resistance to AMX. Moreover, the hydrogel drug carrier is biodegradable, biocompatible, and capable of responding to environmental stimuli, such as pH and the salinity.

The cyclotriphosphazene ring can be opened to form linear polymers which can also be used as antibacterial drug carriers [98-100]. Polyphosphazenes are heteropolymers consisting of alternating phosphorous and nitrogen atoms, where the phosphorous atom is usually connected to two side groups. Cyclotriphosphazene can be thermally opened to form poly(dichlorophosphazene) at 250 °C, and then substituted by various nucleophiles to form polyphosphazenes (**20**, Fig. **19**) [101-105]. For example, the phosphoramide linear polymer can be grafted with fluoroquinolones (*e.g.*, ciprofloxacin or norfloxacin) and ethyl amino acids to form a derivative **20** for antibacterial applications.

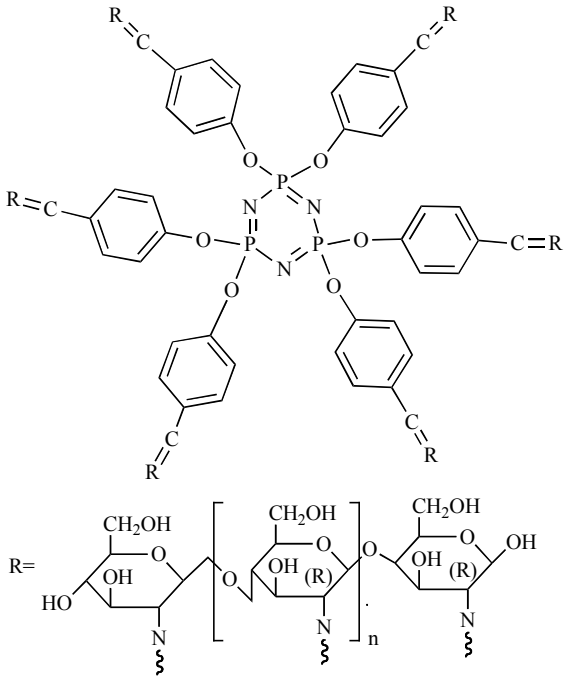


**Fig. (18).** Chemical structure of chitosan hydrogel crosslinked with formyl-phosphazene (**19**). Adapted from reference [97].

In order to increase the solubility of the polymeric polyphosphazene derivatives and control the release rate of antibiotics, the authors attached multiple amino acid ethyl esters (glycine, alanine, and phenylalanine) as co-substituents connected to the polyphosphazene skeleton. The *in vitro* antibacterial experiments showed that ciprofloxacin- and norfloxacin-incorporated **20** had good antibacterial effects on *E. coli* with MIC values of 0.45 μg/mL and 0.58 μg/mL, respectively. These antibacterial activities are equivalent to those of the antibiotics ciprofloxacin and norfloxacin. Meanwhile, an amount of 4–30% antibiotic release was observed in a six-week hydrolysis study at 37 °C, indicating possible localized drug release for prolonged periods from the polymer. The antibiotic release profiles of **20** make it a promising material as a new type of wound dressings.

## CONCLUSION

The research progress in the past 10 years of cyclotriphosphazene derivatives with antibacterial properties is reviewed in this report with representative examples which show that these derivatives, their metal complexes, and polymeric structures with these derivatives as building blocks can all be used in antibacterial applications. Several of these derivatives show good antibacterial activities against a variety of bacteria or can serve as carrier matrix for

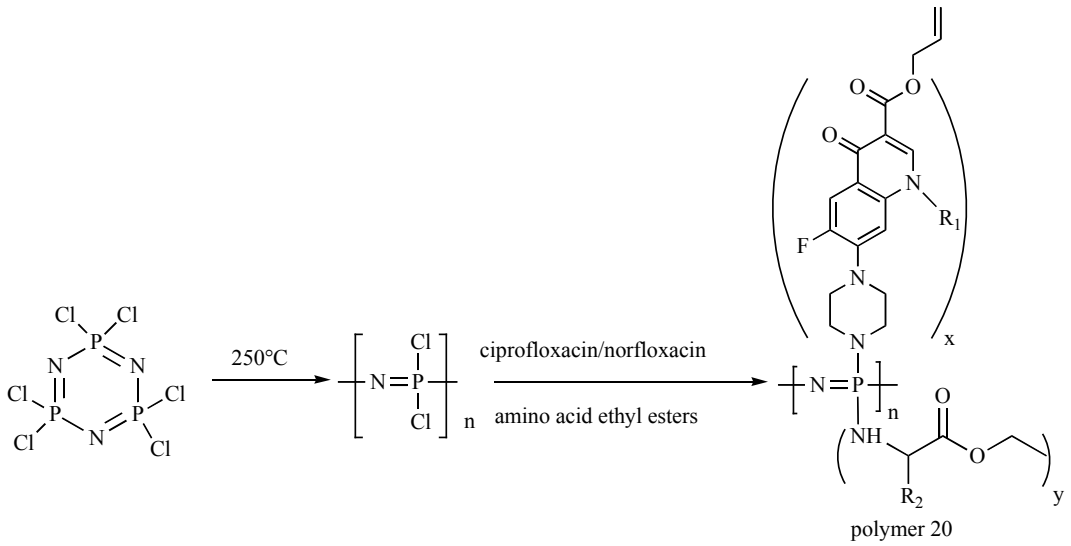



**Fig. (19).** Synthesis and the chemical structure of polymeric **20**. Adapted from reference [105].

delivery of existing antibiotics. These examples point out the opportunities for phosphorous chemistry to take challenging problems in antimicrobial research, such as bacterial resistance. Moreover, the study of the mechanisms for the antibiotic actions of these cyclotriphosphazene derivatives regarding their structure-function relationship will provide valuable knowledge complementary to the existing mechanisms for the action and resistance of better-studies antibiotics.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| HCCP | = | Hexachlorocyclotripolyphosphazene |
| MRSA | = | Methicillin-resistant *Staphylococcus* |
| VRE | = | Vancomycin-resistant *Enterococci* |
| AG | = | Active Groups |
| MIC | = | Minimum inhibitory concentration |
| CP/BZ/Bmi | = | Cyclophosphazene/Benzoxazine/Bismaleimide |
| ATCP/FTiO$_2$/Bz-CE | = | Amine Terminated Cyclotriphosphazene/Functionalized TiO$_2$/Benzoxazine based Cyanate Ester |
| POSS/PZI | = | Polyhedral Oligomeric Silsesquioxane/Phosphazene Polyimide |
| PEI/HCCP | = | Polyethyleneimine/Cyclophosphazene |
| AMX | = | Amoxicillin |
| CPFX | = | Ciprofloxacin |
| NFX | = | Norfloxacin |

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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