Potential antibacterial and antifungal activities of novel sulfamidophosphonate derivatives bearing the quinoline or quinolone moiety

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Abstract
A series of new α-sulfamidophosphonate/sulfonamidophosphonate (4a–n) and cyclosulfamidophosphonate (5a–d) derivatives containing the quinoline or quinolone moiety was designed and synthesized via Kabachnik–Fields reaction in the presence of ionic liquid under ultrasound irradiation. This efficient methodology provides new 1,2,5-thiadiazolidine-1,1-dioxide derivatives 5a–d in one step and optimal conditions. The molecular structures of the novel compounds 4a–n and 5a–d were confirmed using various spectroscopic methods. All these compounds were evaluated for their in vitro antibacterial activity against Gram-negative (Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853) and Gram-positive (Staphylococcus aureus ATCC 27923) bacteria, in addition to three clinical strains (E. coli 1, P. aeruginosa 1, and S. aureus 1). Most of the tested compounds showed more potent inhibitory activities against both Gram-positive and -negative bacteria compared with the sulfamethoxazole reference. The following compounds, 4n, 4f, 4g, 4m, 4l, 4d, and 4e, are the most active sulfamidophosphonate derivatives. Furthermore, these molecules gave interesting zones of inhibition varying between 28 and 49 mm, against all tested bacterial strains, with a low minimum inhibitory concentration (MIC) value ranging from 0.125 to 8 μg/ml. All the synthesized derivatives were also evaluated for their in vitro antifungal activity against Fusarium oxyporum f. sp. lycopersici and Alternaria sp. The results revealed that all the synthesized compounds exhibited excellent antifungal inhibition and the compounds 4f, 4g, 4m, and 4l were the most potent derivatives with MIC values ranging from 0.25 to 1 μg/ml against the two tested fungal strains. The strongest inhibition of bacteria and fungi strains was detected by the effect of quinolone and sulfamide moieties.

KEYWORDS
antibacterial activity, antifungal, quinolone, sulfonamide, α-sulfamidophosphonate

1 | INTRODUCTION

Antimicrobial drugs have caused a remarkable change in the treatment of infectious diseases.[1] There are many ways to get infectious diseases and we are not able to prevent the infections that spread. Every year millions of people are prone to infectious diseases and the death rate is also getting fluctuated due to the intensity of the easily spreading characteristic of the microorganism.[2,3] Currently, antimicrobial chemotherapy made sensational advances to develop new potent antibiotics for combating antimicrobial resistance[4] because...
the microorganism is getting resistant with improvements in existing antibiotic classes by mutation membrane permeability and spore formation to the drugs by adapting themselves to withstand the potency of the drug.\cite{5} Therefore, because of the limiting factor to the effectiveness of current drugs, the development of new treatment approaches and the synthesis of novel, effective, and more potent compounds to be used as chemotherapy is still in demand to overcome these problems.\cite{6,7} In this regard, sulfonamide and cyclosulfamide derivatives have been the focus of attention for chemists and biologists for a long time due to their wide range of biological and physical properties,\cite{8} such as antibacterial,\cite{9,10} anticonvulsant,\cite{11} antihypoglycemic,\cite{12} anticancer,\cite{13} herbicidal,\cite{14} antifungal,\cite{15} as well as their utility as synthetic intermediates.\cite{16}

In search of some new antibiotics, we have focused on sulfonamide and cyclic sulfamide moieties, which have significance in the area of medicinal chemistry\cite{17–21} and drug development and are used as a core substituent of antibacterial agents,\cite{22} for example, the sulfamethoxazole is an available sulfa drug acting as para-aminobenzoic acid competitive inhibitor.\cite{23–25}

Furthermore, a literature review revealed that the presence of quinoline derivatives exhibits good antibacterial activity\cite{26} for the target compound and plays a significant role in the development of new antibacterial agents (Figure 1).\cite{27,28} The great attention paid by researchers to the study of quinoline derivatives is explained by their broad range of biological activities, such as antiviral,\cite{29} antioxidiant, anti-inflammatory,\cite{30} antimicrobial,\cite{31} anti-atherothrombosis,\cite{32} antiemetic,\cite{33} antiulcer,\cite{34} antiallergic,\cite{35} antiaminal, and antiasthmatic\cite{36} and recently, several reports have drawn attention to the use of chloroquine and hydroxychloroquine (antimalarial drugs), as inhibitors of SARS-CoV-2 virus.\cite{37–39}

In contrast, the α-aminophosphonate derivatives show great interest in organic synthesis because of their biological and pharmacological activities.\cite{39} That is why the synthesis of new α-aminophosphonates is underway to find antibiotics,\cite{40} enzyme inhibitors,\cite{41} antileishmanial,\cite{42} antifungal\cite{43} or antitumoral\cite{44} compounds. The current work is an effort to develop novel formulations as effective antibacterial agents against drug-resistant bacterial strains. In this regard, the combination of certain sulfamides/sulfonamides and α-aminophosphonates moiety are very suitable for further modifications to obtain new α-sulfamidophosphonates or α-sulfonamidophosphonates as more cost-effective and more potent, pioneering antibacterial agents with minimum adverse effects\cite{45} (Figure 2).

Owing to such significance and keeping in view the wide range of pharmaceutical activities of sulfonamide, quinoline, and aminophosphonate scaffolds, in this report, we expect that the incorporation of all these moieties in the same scaffold structure may lead to good activities and potent antibacterial agents. Thus, a series of α-sulfamidophosphonate, sulfonamidophosphonate, and cyclosulfamidophosphonate derivatives bearing quinoline or quinolone rings was designed, synthesized, and evaluated for their antibacterial and antifungal activities.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A series of 18 novel α-sulfamidophosphonate (4a–c, 4h–k), α-sulfamidophosphonate (4d–g, 4l–n), and cyclosulfamidophosphonate 5a–d (1,2,5-thiadiazolidine-1,1-dioxide) derivatives containing quinoline or quinolone moiety was designed and synthesized under ultrasound irradiation.

In the first stage, we started our study with the synthesis of aldehyde derivatives and functionalized sulfonamides/sulfamides. The sulfonamides/sulfamides presented in this study as starting materials were obtained from a simple and efficient methodology described in the literature.\cite{46–49} 2-Chloro-quinoline-3-carbaldehyde derivatives 2a–e were obtained via Meth–Cohn reaction,\cite{50} which included the condensation of acetaldehyde derivatives 1a–e with Vilsmeier–Haack reagent. As a continuation, 2-oxoquinoline 3-carbaldehyde derivatives (3a–e) were then obtained in good yields by the hydrolytic reaction of compounds 2a–e in the presence of 70% acetic acid.\cite{51}

In continuation of our program on the development and synthesis of novel compounds of α-aminophosphonate derivatives and to obtain these compounds in high yields and clean conditions, in this study, we have used our previous strategy for the synthesis of new α-sulfamidophosphonate (4a–c, 4h–k), α-sulfamidophosphonate (4d–g, 4l–n), and cyclosulfamidophosphonate 5a–d derivatives in the presence of ionic liquid under ultrasound irradiation. It was

![Figure 1](https://example.com/figure1.png)

**Figure 1** Structures of potent antimicrobial molecules containing quinoline and sulfonamide/sulfamide moieties
previously reported by our research group that in the absence of ionic liquid (triethylammonium acetate [TEAA]), the rates of the reaction were remarkably slowed and the yields were very low. The use of ionic liquid catalyst has gained importance in organic synthesis due to several advantages, such as short reaction time, excellent product yield, low cost, operational and simplicity of the reaction. Owing to the numerous advantages associated with this methodology, the application of ultrasonic irradiation to this reaction increases the efficiency, which otherwise requires a long reaction time. Moreover, ultrasound irradiations are believed to satisfy the demands of "green chemistry" by minimizing waste and reducing energy requirements, allowing for solvent-free conditions to be employed.

Herein, we report a one-pot synthesis of α-sulfamidophosphonate (4a–c, 4h–k), α-sulfamidophosphonate (4d–g, 4l–n) by condensation of quinoline/quinolone carbaldehyde (1 mmol), sulfonamide/sulfamide (1 mmol), and triethylphosphite (1 mmol) catalyzed by ionic liquid (TEAA) and under solvent-free reaction using ultrasound irradiation. This method is an easy, rapid, one-pot, and good-yielding reaction. Thus, this methodology is also suitable for the synthesis of cyclosulfamidophosphonates 5a–d in one step (Scheme 1). The intramolecular cyclization "in situ" is realized in the same conditions and the desired products are obtained with a significant improvement in yield (up to 75%). So, this new methodology of multicomponent condensation reaction in one step is able to promote the synthesis of 1,2,5-thiadiazolidine-1,1-dioxide in short reaction time and ecofriendly conditions. The obtained results are summarized in Table 1.

The structures of target compounds were determined by their spectral data (1H nuclear magnetic resonance [NMR], 13C NMR, 31P NMR, heteronuclear single-quantum coherence [HSQC], heteronuclear multiple bond correlation [HMBC], and elemental analysis). The spectra 1H NMR, 13C NMR, 31P NMR, HSQC, and HMBC 2D NMR are available in the Supplementary Information Material; 1H NMR spectra showed the characteristic signals of four principal types of protons in each product (OC\textsubscript{2}H\textsubscript{2}C\textsubscript{H}3, P\textsubscript{=O}CH\textsubscript{2}N, N\textsubscript{H} and Ar\textsubscript{H}). As expected, in the spectrum, the introduction of phosphonate group is confirmed by the presence of two triplets between 1.09 and 1.48 ppm and two multiplets between 2.81 and 4.52 ppm, representing the protons of CH\textsubscript{3} and CH\textsubscript{2}, respectively, attributed to two methoxy groups of the phosphonate, and the presence of doublet signal characteristic of the proton related to asymmetric carbon P\textsubscript{=O}CH\textsubscript{2}N between 4.9 and 5.6 ppm confirms the condensation of sulfonamide/sulfamide with the quinoline/quinolone carbaldehyde.
Since the peak of N–H protons appeared as two broad singlets, ranged between 3 and 11 ppm only for compounds 4d–g and 4l–n, which have two NH functions of sulfamide group (NH–SO₂–NH). Compounds 4a–c and 4h–k, on the contrary, have one NH function of sulfonamide group (NH–SO₂–R). While, the intramolecular cyclization and the formation of the cycle thia-diazolidine 1,1-dioxide to afford the compounds 5a–e is also confirmed by the absence of a second NH peak and the presence of only broad singlet at 3–5 ppm. Additionally, these compounds revealed a similar singlet signal at 2.80–3.2 ppm that can be assigned to 2NCH₂ protons of the thia-diazolidine scaffold, according to the literature. However, the last type of protons of aromatic rings is located between δ = 6.2 and 8 ppm.

The ¹³C NMR spectra of all compounds were characterized by the presence of new signals of the carbon atoms characteristic of the phosphonate group due to the expected doublets related
| Entry | Aldehyde | Sulfonamide/sulfamide | Time (min) | Yield (%) |
|-------|----------|----------------------|------------|-----------|
| 4a    | ![Image](image1) | ![Image](image2) | 10         | 82        |
| 4b    | ![Image](image3) | ![Image](image4) | 13         | 79        |
| 4c    | ![Image](image5) | ![Image](image6) | 9          | 85        |
| 4d    | ![Image](image7) | ![Image](image8) | 8          | 88        |
| 4e    | ![Image](image9) | ![Image](image10) | 15         | 76        |
| 4f    | ![Image](image11) | ![Image](image12) | 14         | 87        |
| 4g    | ![Image](image13) | ![Image](image14) | 9          | 84        |
| 4h    | ![Image](image15) | ![Image](image16) | 7          | 90        |
| 4i    | ![Image](image17) | ![Image](image18) | 13         | 92        |
| 4j    | ![Image](image19) | ![Image](image20) | 10         | 78        |
| 4k    | ![Image](image21) | ![Image](image22) | 12         | 84        |
| 4l    | ![Image](image23) | ![Image](image24) | 8          | 95        |

(Continues)
to the coupling of the carbon atoms with the phosphorus ($\text{J}_{\text{C-P}}$ couplings; P–O–CH$_2$–CH$_3$), which appear between 16 and 55 ppm and the peak of asymmetric carbon P*CH between 52 and 55 ppm. While, the appearance of peaks between 41 and 45 ppm, characteristic of the two methylene groups, confirmed the formation of 1,2,5-thiadiazolidine ring. In addition, the C atoms of the aromatic ring, which was between the region of $\delta = 113$–130 ppm. Since, the carbonyl (CO) function of characterized compounds containing quinolone moiety appeared at 162–168 ppm.

In the $^{31}$P NMR spectrum, the phosphorus atom was resonated as a single characterized between $\delta = 20$ and 24 ppm approximately in all the synthesized compounds.

The relative attribution of proton–carbon has been determined by a series of 2D NMR, HSQC, and HMBC experiments (400 MHz). 2D mode HSQC experiments confirm the vicinal relationship (C–H correlation 1–2) and the HMBC mode indicates the C–H correlation 1–3.

Elemental analysis furthermore confirms the assigned structures of the synthesized compounds.

All these spectroscopic analyses confirm the obtaining of $\alpha$-sulamidophosphonates/sulfonamidophosphonates and cyclosulfamidophosphonates derivatives targeted in this study.

### 2.2 Biological evaluation

Combinations of two or more active moieties into one scaffold are a common procedure for getting the synergistic effect to enhance the drug activity with less dose of the drug.

Substituted 3-formyl-2-quinolone and 3-formyl-2-quinolones, used in our study as starting materials, have been reported for their antimicrobial and antifungal activities.[54] The literature reports reveal that the quinolone derivatives displayed good antibacterial activity against both Gram-negative and Gram-positive bacterial strains[55] and have immense potential to control methicillin-resistant Staphylococcus aureus infection.[56]

In contrast, the diverse biological activities of $\alpha$-aminophosphonates and sulfamides moieties mentioned above prompted us to test the antibacterial activities of the novel synthesized products. Hence, the
18 newly synthesized compounds were screened for their in vitro antimicrobial activity against selected strains of Gram-positive and -negative bacteria as well as two fungal strains.

2.2.1 | In vitro antibacterial activity

The sulfamidophosphonate/sulfamidophosphonate and cyclosulfamidophosphonate derivatives were evaluated for their in vitro antibacterial activity against six bacterial strains causing several infectious diseases, four strains are Gram-negative: *Escherichia coli* (ATCC 25922), *E. coli* 1, *Pseudomonas aeruginosa* (ATCC 27853), and *P. aeruginosa* 1, in addition to two Gram-positive strains, *S. aureus* (ATCC 27923) and *S. aureus* 1. Dimethyl sulfoxide (DMSO) was used as a negative control and the commercial antibiotic sulfamethoxazole as a positive control.

Initially, in vitro antibacterial activity of the α-sulfamidophosphonate (4a-c, 4h-k), α-sulfamidophosphonate (4d-g, 4l-n), and cyclosulfamidophosphonate 5a-e derivatives was evaluated by agar well diffusion assay\(^ {57}\) using a concentration of 512 µg/ml. Subsequently, the zone of inhibition was measured in millimeters. The results are presented in Table 2.

To further determine the antibacterial effect of the tested compounds, the minimum inhibitory concentration (MIC) values and the minimum bactericidal concentration (MBC) against the above-mentioned bacterial strains were measured by a broth dilution method\(^ {58-60}\). The MIC value is defined as the lowest concentration of antibacterial agent that inhibits visible growth and the MBC value is the higher antibiotic concentration that will kill the organisms. The MIC and MBC values are summarized in Table 3.

It is obviously observed from the obtained results that all the newly synthesized compounds showed high antibacterial activity compared with the sulfamethoxazole reference (positive control). The diameters of inhibition zone (DIZ) values obtained with the positive control sulfamethoxazole ranged between 6 and 12 mm against Gram-positive and -negative strains and with MIC value of 64 µg/ml against *E. coli* ATCC 25922 and 128 µg/ml against *E. coli*

### Table 2: Diameters of the inhibition zone (DIZ) of α-sulfamidophosphonate/sulfamidophosphonate and cyclosulfamidophosphonate derivatives

| Molecules | Diameters of inhibition zone (mm) | Gram-negative strains | Gram-positive strains |
|-----------|----------------------------------|-----------------------|----------------------|
|           | *Escherichia coli* ATCC 25922 | *Escherichia coli* 1 | *Pseudomonas aeruginosa* ATCC 27853 | *Pseudomonas aeruginosa* 1 | *Staphylococcus aureus* ATCC 27923 | *Staphylococcus aureus* 1 |
| 4a        | 10                               | 9                     | 20                   | 22                   | 14                   | 10 |
| 4b        | 6                                 | 8                     | 12                   | 10                   | R                    | 11 |
| 4c        | 11                                | 7                     | 16                   | 9                    | 11                   | 19 |
| 4d        | 32                                | 29                    | 30                   | 29                   | 28                   | 29 |
| 4e        | 34                                | 30                    | 32                   | 30                   | 29                   | 30 |
| 4f        | 42                                | 33                    | 37                   | 39                   | 40                   | 36 |
| 4         | 38                                | 35                    | 34                   | 32                   | 35                   | 33 |
| 4h        | 26                                | 25                    | 25                   | 22                   | 20                   | 24 |
| 4i        | 30                                | 28                    | 27                   | 31                   | 29                   | 27 |
| 4j        | 28                                | 30                    | 29                   | 30                   | 27                   | 26 |
| 4k        | 27                                | 29                    | 26                   | 27                   | 25                   | 27 |
| 4l        | 35                                | 33                    | 34                   | 32                   | 30                   | 33 |
| 4m        | 36                                | 32                    | 37                   | 34                   | 33                   | 35 |
| 4n        | 49                                | 38                    | 36                   | 43                   | 49                   | 42 |
| 5a        | 11                                | 18                    | 6                    | 9                    | 7                    | R |
| 5b        | 16                                | 12                    | 10                   | R                    | R                    | R |
| 5c        | 25                                | 27                    | 23                   | 19                   | 9                    | 7 |
| 5d        | 32                                | 22                    | 25                   | 27                   | 13                   | 10 |
| Sulfamethoxazole\(^{a}\) | 12 | 11 | 9 | 6 | R | R |

Abbreviation: R, resistant.

\(^{a}\)Positive reference.
Table 3: MICs and MBCs of sulfamidophosphonate/sulfonamidophosphonate (4a-n) and cyclosulfamidophosphonate (5a-d) derivatives

| Molecules | Escherichia coli ATCC 25922 |  | Escherichia coli 1 |  | Staphylococcus aureus ATCC 27923 |  | Staphylococcus aureus 1 |  | Pseudomonas aeruginosa ATCC 27853 |  | Pseudomonas aeruginosa 1 |
|-----------|----------------------------|---|--------------------|---|-----------------|---|-----------------|---|-------------------|---|-------------------|
|           | MIC (µg/ml) | MBC (µg/ml) | R | MIC (µg/ml) | MBC (µg/ml) | R | MIC (µg/ml) | MBC (µg/ml) | R | MIC (µg/ml) | MBC (µg/ml) | R | MIC (µg/ml) | MBC (µg/ml) | R |
| 4a        | 128          | 256          | 2 | 64           | 128          | 2 | 256           | 512          | 2 | 64           | 128          | 2 | 256           | 512          | 2 |
| 4b        | 128          | 256          | 2 | 32           | 64           | 2 | 128           | 512          | 4 | 256           | 512          | 2 | –             | –             | – |
| 4c        | 64           | 128          | 2 | 128          | 256          | 2 | 64           | 256          | 4 | 128           | 512          | 4 | 128           | 512          | 4 |
| 4d        | 1            | 4            | 4 | 0.5          | 2            | 4 | 1             | 4            | 4 | 2             | 8            | 4 | 2             | 8            | 4 |
| 4e        | 0.5          | 2            | 4 | 2            | 16           | 8 | 1             | 2            | 2 | 1             | 4            | 4 | 2             | 4            | 2 |
| 4f        | 0.125        | 1            | 8 | 0.125        | 1            | 8 | 0.25          | 1            | 4 | 0.25          | 2            | 8 | 0.5           | 2            | 4 |
| 4g        | 0.5          | 4            | 8 | 0.25         | 1            | 4 | 0.5           | 1            | 2 | 0.25          | 1            | 4 | 0.5           | 1            | 2 |
| 4h        | 8            | 32           | 4 | 8            | 32           | 4 | 8             | 16           | 128         | 8  | 8             | 32           | 2 | 64           | 128          | 2 |
| 4i        | 2            | 4            | 2 | 1            | 4            | 2 | 4             | 2            | 4 | 4             | 32           | 8 | 8             | 16           | 2 |
| 4j        | 2            | 8            | 4 | 4            | 16           | 4 | 2             | 8            | 4 | 4             | 8            | 2 | 16           | 64           | 4 |
| 4k        | 4            | 8            | 2 | 2            | 4            | 2 | 4             | 8            | 2 | 8             | 64           | 8 | 32           | 64          | 2 |
| 4l        | 0.5          | 1            | 2 | 1            | 8            | 8 | 0.5           | 2            | 4 | 1             | 2            | 2 | 1             | 4            | 4 |
| 4m        | 0.5          | 4            | 8 | 0.5          | 2            | 4 | 1             | 8            | 8 | 0.5           | 2            | 4 | 1             | 2            | 2 |
| 4n        | 0.125        | 1            | 8 | 0.125        | 0.5          | 2 | 0.5           | 2            | 4 | 0.125         | 1            | 8 | 0.25          | 1            | 4 |
| 5a        | 128          | 256          | 2 | 128          | 256          | 2 | 64           | 128          | 2 | 128           | 512          | 4 | 256           | 512          | 2 |
| 5b        | 256          | 512          | 2 | 256          | 512          | 2 | 128          | 256          | 2 | –             | –             | – | –             | –             | – |
| 5c        | 32           | 128          | 4 | 64           | 512          | 8 | 128          | 256          | 2 | 64           | 256          | 4 | 128           | 512          | 4 |
| 5d        | 16           | 64           | 4 | 8            | 16           | 2 | 32           | 64           | 2 | 64           | 256          | 4 | 128           | 256          | 2 |

Abbreviations: MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; –, no inhibition (or concentration >512 µg/ml).

R = MBC/MIC.

1. S. aureus ATCC 27923, and S. aureus 1. Whereas P. aeruginosa ATCC 27853 and P. aeruginosa 1 strains were resistant toward sulfa- methoxazole standard. The negative control (DMSO) did not show any antibacterial activity.

The results reveal that the compounds 4n, 4f, 4g, 4i, 4l, and 4e, respectively, showed the highest antibacterial activity and excellent inhibition against all bacterial strains with inhibition zone (DIZ) values between 28 and 49 mm, and MIC values ranging from 0.125 to 8 µg/ml, for both clinical and reference strains. It can be clearly seen that these derivatives contained a sulfamide function (NH–SO2–NH) and had respectively ortho-methoxyl, para-bromo, para-fluoro, and para-methyl substituents attached to the sulfamide ring, which exhibited strong electron-donating and/or electron-withdrawing properties,[25] which might have plausibly contributed to the potent antibacterial activity of these compounds.

Another series of compounds, 4h–k, bearing sulfonamide function (NH–SO2–R) and quinolone moiety, also showed excellent activity against Gram-negative strains, E. coli ATCC 25922, E. coli 1, S. aureus ATCC 27923, and S. aureus 1 with MIC values ranging from 1–16 µg/ml and with DIZ values between 20 and 31 mm, whereas good-to-moderate activity against strains P. aeruginosa and P. aeruginosa 1 (8 µg/ml ≤ MIC ≤ 64 µg/ml). All these compounds exhibited a higher inhibition zone than the standard antibiotic sulfamethoxazole against all tested bacterial strains. 4i was the most active among this series, probably due to the presence of para-methyl substituent attached to the quinolone scaffold. These derivatives showed better results than 4c, 4b, and 4a (32 µg/ml ≤ MIC ≤ 256 µg/ml), which have a quinolone moiety. From this point, it is noticeably evident that the antibacterial activity was highly dependent on the nature of the ring substituent as well as the chemical nature of the substituents and their positions on the sulfamide or sulfonamide ring. In general, compounds containing a sulfamide group possessed much higher activity than those containing a sulfonamide group. However, the newly synthesized sulfamidophosphonate derivatives bearing quinolone moiety were the most active and demonstrated a high antibacterial activity compared with those bearing quinolone moiety, especially against Gram-negative bacterial strains.
the nature of the tested microbial strains as they were multidrug-resistant, particularly for sulfamethoxazole. Compounds 5a and 5b bearing quinoline scaffold exhibited moderate activity against both Gram-negative and -positive bacteria (64 μg/ml ≤ MIC ≤ 256 μg/ml). This remark confirms our previous results about the effectiveness of quinoline moiety compared with the quinoline ring. It is important to note that all sulfamidophosphonate and sulfonamidophosphonate products 4a–n exhibit greater antibacterial activity than the cyclosulfamidophosphonate derivatives 5a–d against both Gram-positive and -negative strains.

It is worth noting that high MIC values might be attributed to the nature of the tested microbial strains as they were multidrug-resistant, particularly for sulfamethoxazole.

However, the MBC of the tested molecules was determined to define the action of an antibacterial on the bacterial strains using the ratio MBC/MIC. If the ratio MBC/MIC ≤ 4, the effect was considered as bactericidal, but if the ratio MBC/MIC > 4, the effect was defined as bacteriostatic.[61,62]

Overall, the MBC values of all tested compounds were found to be between 0.5 and 512 μg/ml and the bactericidal and bacteriostatic effect of the tested compounds was determined using the ratio MBC/MIC. Most of the synthesized molecules showed the ratio MBC/MIC ≤ 4, which may be classified as bactericidal agents, especially for the compounds 4a, 4b, 4c, 4d, 4j, and 5d, which showed the ratio MBC/MIC ≤ 4 on all tested bacterial strains, suggesting that these molecules act as bactericidal agents against both Gram-positive and -negative strains. Also, we observed that all the synthesized compounds have a bactericidal effect (R ≤ 4) against Gram-positive strains, and a minority of products that have demonstrated a bacteriostatic effect, such as the derivatives 4f, 4g, 4m, 4n against E. coli ATCC 25922 and 4e, 4f, 4h, 4i, 5c against E. coli 1, in addition to 4h, 4f toward S. aureus ATCC 27923, and 4f, 4i, 4k, and 4n versus S. aureus 1, these derivatives achieved a ratio MBC/MIC = 8 ± 4.

It could be concluded that the presence of quinoline-aminophosphonate moiety in the same scaffold with sulfamide/sulfonamide group significantly increases the antibacterial activity against all tested bacterial strains. Subsequently, all the novel synthesized compounds 4a–n and 5a–d exhibited a broad spectrum of antimicrobial activity and these derivatives can be considered as promising antibacterial agents. Comparison of antibacterial activity of all newly synthesized compounds with reference antibiotic sulfamethoxazole is shown in Figure 3.

2.2.2 | In vitro antifungal activity

Antifungal activity of 18 newly synthesized compounds was determined in vitro against two phytopathogenic fungi strains, namely Fusarium oxysporum f. sp. lycopersici (FOL) and Alternaria sp. These strains were tested for fungi toxicity by evaluating mycelia growth inhibition of pathogenic agents. The inhibitory activity of the various compounds, on the mycelium growth of the two phytopathogenic agents, is determined by measuring the diameter growth of the fungus on potato dextrose agar (PDA) medium containing the tested product. DMSO was considered as negative control and amphotericin B as a positive control. The negative control contains PDA and DMSO without any other products.

The mycelial growth of the phytopathogenic agent is measured at a millimetric scale after 7 days of incubation at 25°C. The results were expressed as the percentage of growth inhibition of each fungus grown in the control medium. Thus, the inhibition activity was expressed as a percentage and was calculated according to the formula: Inhibition
The inhibition zones of the test compounds were compared with controls. The percentage of growth inhibition at 64 µg/ml concentration of tested compounds and the MIC values of in vitro antifungal activity results of all starting materials and reagents used for synthesis were obtained commercially from commercial sources Sigma-Aldrich and Acros and Abbreviation: MIC, minimum inhibitory concentration.

| Molecules | Fusarium oxysporum f. sp. lycopersici | Alternaria sp. |
|-----------|-----------------------------------|----------------|
|           | Percentage inhibition (%)<sup>a</sup> | MIC (µg/ml) | Percentage inhibition (%)<sup>a</sup> | MIC (µg/ml) |
| 4a        | 78.14 ± 0.01                      | 8             | 60.74 ± 0.09            | 16           |
| 4b        | 71.06 ± 0.25                      | 5             | 59.62 ± 0.09            | 16           |
| 4c        | 77.61 ± 0.08                      | 8             | 64.44 ± 0.04            | 8            |
| 4d        | 79.22 ± 0.10                      | 1             | 62.59 ± 0.26            | 0.5          |
| 4e        | 73.25 ± 0.32                      | 0.5           | 56.29 ± 0.02            | 2            |
| 4f        | 89.62 ± 0.61                      | 0.125         | 70.47 ± 0.12            | 0.25         |
| 4g        | 90.12 ± 0.20                      | 0.125         | 72.66 ± 0.38            | 0.25         |
| 4h        | 73.25 ± 0.50                      | 4             | 69.96 ± 0.88            | 4            |
| 4i        | 85.38 ± 0.09                      | 0.125         | 71.78 ± 0.10            | 1            |
| 4j        | 76.66 ± 0.37                      | 1             | 65.36 ± 0.39            | 2            |
| 4k        | 71.11 ± 0.07                      | 2             | 69.46 ± 0.22            | 2            |
| 4l        | 78.88 ± 0.72                      | 0.5           | 70.59 ± 0.02            | 4            |
| 4m        | 86.32 ± 0.24                      | 0.125         | 76.84 ± 0.09            | 0.25         |
| 4n        | 84.29 ± 0.49                      | 0.5           | 81.46 ± 0.17            | 0.25         |
| 5a        | 62.22 ± 0.15                      | 2             | 68.32 ± 0.31            | 8            |
| 5b        | 68.58 ± 0.34                      | 4             | 73.58 ± 0.22            | 4            |
| 5c        | 70.04 ± 0.06                      | 1             | 71.25 ± 0.78            | 4            |
| 5d        | 69.87 ± 0.20                      | 1             | 69.45 ± 0.88            | 8            |

Amphotericin<sup>b</sup> 15 ± 0.10 256 38 ± 0.07 64

Abbreviation: MIC, minimum inhibitory concentration.

<sup>a</sup>Values are the means of three replicates ± SD.

<sup>b</sup>Positive control.

% = (C – T/C) × 100, where C is the colony diameter of a phytopathogenic agent in millimeters on the PDA medium with DMSO (control), and T is the colony diameter in millimeters of the phytopathogenic agent on PDA medium containing the tested compound. The inhibition zones of the test compounds were compared with controls.

The percentage of growth inhibition at 64 µg/ml concentration of tested compounds and the MIC values of in vitro antifungal activity was determined and is illustrated in Table 4.

According to the results (Table 3), the negative control did not show any antifungal activity and the positive control amphotericin showed weak-to-moderate activity against FOL and Alternaria sp. The inhibition percentages and the MIC values of amphotericin reference were in the range of 15 ± 0.10 to 38 ± 0.07% and 64–256 µg/ml against both tested fungal strains. All tested compounds displayed excellent antifungal activity against both fungi strains (FOL and Alternaria sp.) compared with the amphotericin reference with MIC values ranging between 0.125 and 16 µg/ml and with inhibition percentages varied from 59.62 ± 0.09 to 90.12 ± 0.20% at the concentration of 64 µg/ml. Compounds 4f, 4g, 4m, and 4i were the most potent derivatives with MIC value of 0.125 µg/ml against FOL and with MIC values ranging from 0.25 to 1 µg/ml against Alternaria sp. While, the compounds 4e, 4l, 4n, 4g, and 4d also showed excellent inhibition and exhibited an MIC value between 0.5 and 2 µg/ml against both tested fungal strains in this study.

In conclusion, the newly synthesized sulfamidophosphonate/sulfonamidophosphonate 4a–n and cyclosulfamidophosphonate 5a–d derivatives bearing quinoline or quinolone heterocycle, showed potent antibacterial activity against multidrug-resistant strains of Gram-positive and Gram-negative bacteria, and they are also effective against fungi FOL and Alternaria sp. These compounds could attract the interest of researchers for the treatment of serious infectious diseases caused by multidrug-resistant microbial strains.

### 3 | CONCLUSION

New sulfamidophosphonate, sulfonamidophosphonate, and cyclosulfamidophosphonate derivatives bearing quinoline or quinolone moiety were synthesized and evaluated for their antibacterial and antifungal activities. Therefore, these molecules presented a significant antibacterial activity on Gram-positive and Gram-negative strains as compared with the sulfamethoxazole control. Compounds 4n, 4f, 4g, 4m, 4l, 4d, and 4e, respectively, containing a sulfamide function, showed the best inhibition against clinical and reference strains with MIC values ranging from 0.125 to 8 µg/ml. Besides this, all sulfamidophosphonate and sulfonamidophosphonate products 4a–n exhibited stronger activity than the cyclosulfamidophosphonate derivatives 5a–d against both Gram-positive and Gram-negative strains and most of these new compounds presented a bactericidal effect. In contrast, the antifungal assay revealed that all the synthesized compounds 4a–n and 5a–d displayed excellent-to-good inhibition of the two phytopathogenic fungi strains, FOL and Alternaria sp. with MIC values ranging between 0.125 and 16 µg/ml compared with the amphotericin standard.

It can be concluded that all the synthesized compounds showed potent antimicrobial activities against all tested pathogenic bacteria and fungi strains. Subsequently, these results can help researchers to look for new potent antimicrobial agents for therapeutic use.

### 4 | EXPERIMENTAL

#### 4.1 | Chemistry

#### 4.1.1 | General

All starting materials and reagents used for synthesis were obtained commercially from commercial sources Sigma-Aldrich and Acros and...
were used without purification. Sonication was performed in a Fungilab ultrasonic bath with a frequency of 40 kHz and output power of 250 W. Melting points were measured using Buchi Melting Point B-545. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and ninhydrin solution as developing agents. 1H NMR and 13C NMR spectra were recorded at 25°C on Bruker spectrometers (400 MHz for 1H, 101 MHz for 13C, and 162 MHz for 31P) using tetramethylsilane as internal standard and CDCl3 or DMSO as solvent. Elemental analysis (C, H, and N) were performed on a PerkinElmer 6 as solvent.

4.1.3 | General procedure for the synthesis of quinoline derivatives

Place dimethylformamide (3 eq) in a flask equipped with a drying tube cooled to 0°C temperature, then phosphorus oxychloride (POCl3; 7 eq) was added dropwise with stirring to it. To this solution, add acetonilide (1 mmol). After a few minutes, the reaction mixture was refluxed for 6–8 h. After completion of the required time reaction, the mixture was cooled and poured in ice-cold water and stirred for about half an hour, and then filtered to offer powdered compound.

2-Chloro-3-formyl-6-methylquinoline
C11H8CINO; MW = 205.64; TLC Rf = 0.43 (CH2Cl2); yellow powder; mp: 176–177°C; 75% yield; IR νmax (KBr) (cm⁻¹) = 1645 (CO). 1H NMR (400 MHz, DMSO-d6) δ 10.57 (s, 1H, CHO), 8.58 (s, 1HAr), 7.97 (d, Jortho = 7.7 Hz, 1HAr), 7.75 (d, Jmeta = 2.3 Hz, 1HAr), 7.74 (dd, Jortho = 7.7, Jmeta = 2.4 Hz, 1HAr), 2.57 (s, 3H, CH3) ppm. 13C NMR (101 MHz, DMSO-d6) δ = 189.3, 149.2, 148.1, 139.5, 138.4, 135.9, 128.3, 128.1, 126.5, 126.2, 21.5 ppm.

4.1.4 | General procedure for the preparation of compounds 3a–f

2-Chloro-3-formyl quinoline derivatives (2a–f) were treated with 70% acetic acid aqueous solution (200 ml) at 95°C for 10 h and then the solution was cooled to room temperature to offer needle crystals of compounds 3a–f.

6-Methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (3b)
C11H10NO2; MW = 187.20; TLC Rf = 0.35 (CH2Cl2); yellow powder; mp: 205–206°C; 92% yield. 1H NMR (400 MHz, DMSO-d6) δ 12.11 (s, 1H, NH), 10.24 (s, 1H, CHO), 8.40 (s, 1HAr), 7.71–7.65 (m, 1HAr), 7.49 (dd, Jortho = 8.4, Jmeta = 2.0 Hz, 1HAr), 7.27 (dd, Jortho = 8.4 Hz, 1HAr), 2.35 (s, 3H, CH3Ar) ppm. 13C NMR (101 MHz, DMSO-d6) δ = 190.25, 161.79, 142.52, 139.75, 135.57, 132.22, 130.47, 126.05, 118.55, 115.81, 20.73 ppm.

4.1.5 | General procedure for the preparation of α-sulfamidophosphonates/sulfonamidophosphonates 4a–n and cyclosulfamidophosphonates 5a–d

In a 10-ml round-bottom flask, a mixture of sulfamide/sulfonamide (1 mmol) and aldehyde (1 mmol) was taken with 1 ml of ionic liquid at room temperature, then triethylphosphite (1 mmol) was added. The reaction mixture was subjected to ultrasonication for an appropriate time. After completion of the reaction, as indicated by TLC, distilled water was added. The product was finally filtered and dried and it was purified by recrystallization using chloroform/diethyl ether to yield pure α-sulfamidophosphonates/sulfonamidophosphonates 4a–n and cyclosulfamidophosphonates 5a–d.

Diethyl[(2-chloroquinolin-3-yl)[(4-methylphenyl)sulfamoyl]methyl]phosphonate (4a)
C21H24ClN2O5PS, MW = 482.92; TLC Rf = 0.51 (CH2Cl2/MeOH 7:3); yellow powder; mp: 162–163°C; 82% yield. 1H NMR (400 MHz, chloroform-d6) δ 11.82 (s, 1H, NH), 8.02 (d, J = 3.6 Hz, 1HAr), 7.83 (dd, Jortho = 8.9, Jmeta = 2.8 Hz, 2HAr), 7.66–7.53 (m, 1HAr), 7.60 (td, Jortho = 8.8, Jmeta = 2.3 Hz, 1H), 7.50 (td, Jortho = 7.9, Jmeta = 1.5 Hz, 1HAr), 7.38 (d, J = 8.3, 1HAr), 7.27 (s, 1HAr), 7.22 (td, Jortho = 7.5, Jmeta = 2.1 Hz, 1HAr), 7.15 (t, J = 7.3 Hz, 1HAr), 4.79 (d, J = 6.4 Hz, 2H), 2.68 (s, 2H, PCH3), 4.34–4.15 (m, 2H, OCH2CH3), 3.13–2.84 (m, 2H, OCH2CH3), 2.40 (s, J = 7.3 Hz, 3H, CH3–Ar), 1.32 (t,
$J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.22 (t, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$) ppm. $^{13}$C NMR (101 MHz, chloroform-d$_6$) δ 163.10, 143.32, 139.46, 139.28, 139.21, 137.52, 130.86, 129.61 (2CH), 128.20, 127.28, 126.39 (2CH), 123.13, 119.85 (d, $J_{C-P} = 2.7$ Hz), 67.51 (d, $J_{C-P} = 161.6$ Hz), 63.48 (d, $J_{C-P} = 7.0$ Hz), 31P NMR (162 MHz, CDCl$_3$) δ 21.10 ppm. Anal. calcld. for C$_{21}$H$_{25}$FN$_3$O$_6$PS (497.48): C, 50.70; H, 5.07; F, 3.82; N, 5.81; O, 16.42; P, 6.65; S, 6.48%. Diethyl[(2-chloro-7-methylquinolin-3-yl)⁃(N⁃p⁃tolyl)sulfamoyl]amino)methyl]phosphonate (4d) C$_{22}$H$_{27}$ClN$_3$O$_5$PS, MW = 511.96; TLC $R_f = 0.66$ (CH$_2$Cl$_2$/MeOH 7:3); yellow powder; mp: 170–171°C; 88% yield; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 9.57 (s, 1H, NH), 8.86 (dd, $J_{H,P} = 11.3$, $J = 6.9$ Hz, 1H, NH), 8.26 (d, $J = 4.8$ Hz, 1HAr), 7.63 (d, $J = 2.2$ Hz, 1HAr), 7.47 (dd, $J_{ortho} = 11.8$, $J_{meta} = 4.8$ Hz, 1H), 7.42 (dd, $J = 8.8$, 1.7 Hz, 1HAr), 6.66 (d, $J_{ortho} = 10.1$ Hz, 2HAr), 6.51 (d, $J_{meta} = 25.5$ Hz), 5.34; N, 10.12; O, 23.11; P, 7.46; S, 7.72%; found: C, 46.35; H, 5.46; N, 6.01; O, 20.70; P, 6.65; S, 6.48%. Diethyl[(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)[(2-oxo-1,2-di hydroquinolin-3-yl)methyl]phosphonate (5e) C$_{16}$H$_{12}$N$_2$O$_4$PS, MW = 415.40; TLC $R_f = 0.42$ (CH$_2$Cl$_2$/MeOH 7:3); white powder; mp: 126–127°C; 81% yield. $^1$H NMR (400 MHz, chloroform-d$_6$) δ 12.22 (s, 1H, NH), 8.07 (d, $J = 3.7$ Hz, 1HAr), 7.57 (dd, $J_{ortho} = 7.9$, $J_{meta} = 2.2$ Hz, 1HAr), 7.48 (dd, $J_{ortho} = 9.5$, 7.7, $J_{meta} = 2.4$ Hz, 1HAr), 7.39 (d, $J_{ortho} = 7.7$ Hz, 1HAr), 7.26–7.16 (m, 1HAr), 5.82 (s, 1H, NH), 5.67 (d, $J_{H,P} = 12.6$ Hz, 1H, P*CH), 4.34–4.04 (m, 4H, OCH$_2$CH$_3$), 2.04 (s, 4H, NCH$_2$CH$_2$N), 1.30 (t, $J = 7.5$ Hz, 3H, OCH$_2$CH$_3$), 1.23 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$) ppm. $^{13}$C NMR (101 MHz, chloroform-d$_6$) δ 163.18 (d, $J_{C-P} = 4.4$ Hz), 139.25 (d, $J_{C-P} = 7.0$ Hz), 137.56, 130.75, 128.20 (d, $J_{C-P} = 11.7$ Hz), 127.68 (d, $J_{C-P} = 6.2$ Hz) 123.02, 119.88 (d, $J_{C-P} = 2.9$ Hz), 115.86, 66.20 (d, $J_{C-P} = 163.2$ Hz), 63.54 (d, $J_{C-P} = 7.0$ Hz), 63.42 (d, $J_{C-P} = 7.3$ Hz), 45.17, 21.91, 16.43, 16.37 ppm. $^{31}$P NMR (162 MHz, CDCl$_3$) δ 21.35 ppm. Anal. calcld. for C$_{16}$H$_{22}$N$_3$O$_6$PS (415.40): C, 46.26; H, 5.35; N, 10.12; O, 23.13; P, 7.45; S, 7.71%; found: C, 46.28; H, 5.35; N, 10.12; O, 23.13; P, 7.45; S, 7.71%.

4.2 | Biological assays

4.2.1 | Antibacterial activity

The in vitro antibacterial activity of all synthesized compounds was assayed against Gram-positive and -negative bacteria (S. aureus (ATCC 25923), E. coli (ATCC 25922), and P. aeruginosa (ATCC 27853)), in addition to three clinical strains (E. coli 1, S. aureus 1, and P. aeruginosa 1) according to agar disc diffusion method on solid medium Mueller–Hinton.[53] DMSO was used as a negative control and the antibacterial agent sulfamethoxazole as a positive control. The DIZ of each product was measured in millimeters in accordance with the recommendations of the Clinical and Laboratory Standards Institute.[63]

Serial dilutions of the tested compounds were prepared in DMSO in a concentration range from 0.125 to 512 𝜇g/ml. All tests
were performed in triplicate. The MIC and the MBC values of tested molecules were determined using broth dilution method after incubation at 37°C and observed for bacterial growth after 24 h for MIC and 96 h (4 days) for MBC determinations after inoculation for 24 h.

4.2.2 | Antifungal activity

Antifungal activity of 18 newly synthesized compounds was determined in vitro against two phytopathogenic fungi strains (FOL and Alternaria sp.). The inhibitory activity of the various compounds on the mycelium growth of the two phytopathogenic agents is determined by measuring the colony diameter of the fungus on PDA medium, containing the tested product. Amphotericin B was considered as a positive control. The experiment is replicated three times for each compound. After 7 days of incubation at 25°C, the colony diameter of phytopathogenic agent is measured at a millimetric scale. The results were expressed as the percentage of growth inhibition of each fungus grown in the control medium. Thus, the inhibition activity was expressed as a percentage and was calculated according to the formula: Inhibition % = (C - T/C) × 100, where C is the colony diameter of the phytopathogen agent in millimeters on the PDA medium with DMSO (control) and T is the colony diameter in millimeters of the phytopathogenic agent on PDA medium containing the tested compound. The inhibition zones of the test compounds were compared with controls.

To identify the lowest inhibitory concentration, the test was repeated with serial dilutions of each product in a concentration range from 0.125 to 512 µg/ml.[64,65]

ACKNOWLEDGMENTS

This study was supported by The General Directorate for Scientific Research and Technological Development (DG-RSDT), Algerian Ministry of Scientific Research, Algeria.

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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How to cite this article: Bazine I, Bendjedid S, Boukhari A. Potential antibacterial and antifungal activities of novel sulfamidophosphate derivatives bearing the quinoline or quinolone moiety. Arch Pharm. 2021;354:e2000291. https://doi.org/10.1002/ardp.202000291