Received: 6 August 2020 | Revised: 1 October 2020 | Accepted: 6 November 2020

DOI: 10.1002/ardp.202000291

FULL PAPER

ARCH PHARM DPhG
Archiv der Pharmazie

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 **4i** 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.[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 chemotherapeutics is still in demand to overcome these problems.[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,[8] such as antibacterial,[9,10] anticonvulsant,[11] antihypoglycemic,[12] anticancer,[13] herbicidal,[14] antifungal,[15] as well as their utility as synthetic intermediates.[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[17–21] and drug development and are used as a core substituent of antibacterial agents,[22] for example, the sulfamethoxazole is an available sulfa drug acting as *para*-aminobenzoic acid competitive inhibitor.[23–25]

Furthermore, a literature review revealed that the presence of quinoline derivatives exhibits good antibacterial activity[26] for the target compound and plays a significant role in the development of new antibacterial agents (Figure 1).[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,[29] antioxidant, anti-inflammatory,[30] antimicrobial,[31] anti-atherothrombosis,[32] antiemetic,[33] anxiolytic,[34] antimalarial, and antileishmanial,[35] and recently, several reports have drawn attention to the use of chloroquine and hydroxychloroquine (antimalarial drugs), as inhibitors of SARS-CoV-2 virus.[36–38]

In contrast, the α-aminophosphonate derivatives show great interest in organic synthesis because of their biological and pharmacological activities.[39] That is why the synthesis of new α-aminophosphonates is underway to find antibiotics,[40] enzyme inhibitors,[41] antileishmanial,[42] antifungal,[43] or antitumoral[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[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-sulfonamidophosphonate (**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.[46–49] 2-Chloro-quinoline-3-carbaldehyde derivatives **2a–e** were obtained via Meth–Cohn reaction,[50] which included the condensation of acetanilide 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.[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-sulfonamidophosphonate (**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

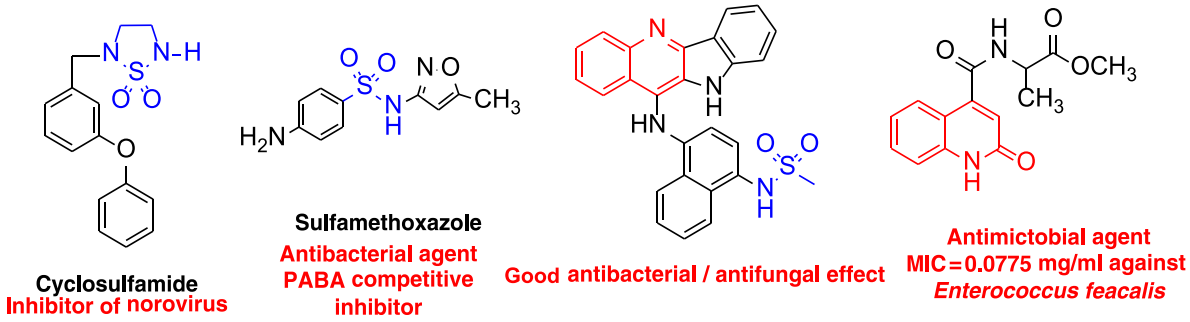


FIGURE 1 Structures of potent antimicrobial molecules containing quinoline and sulfonamide/sulfamide moieties

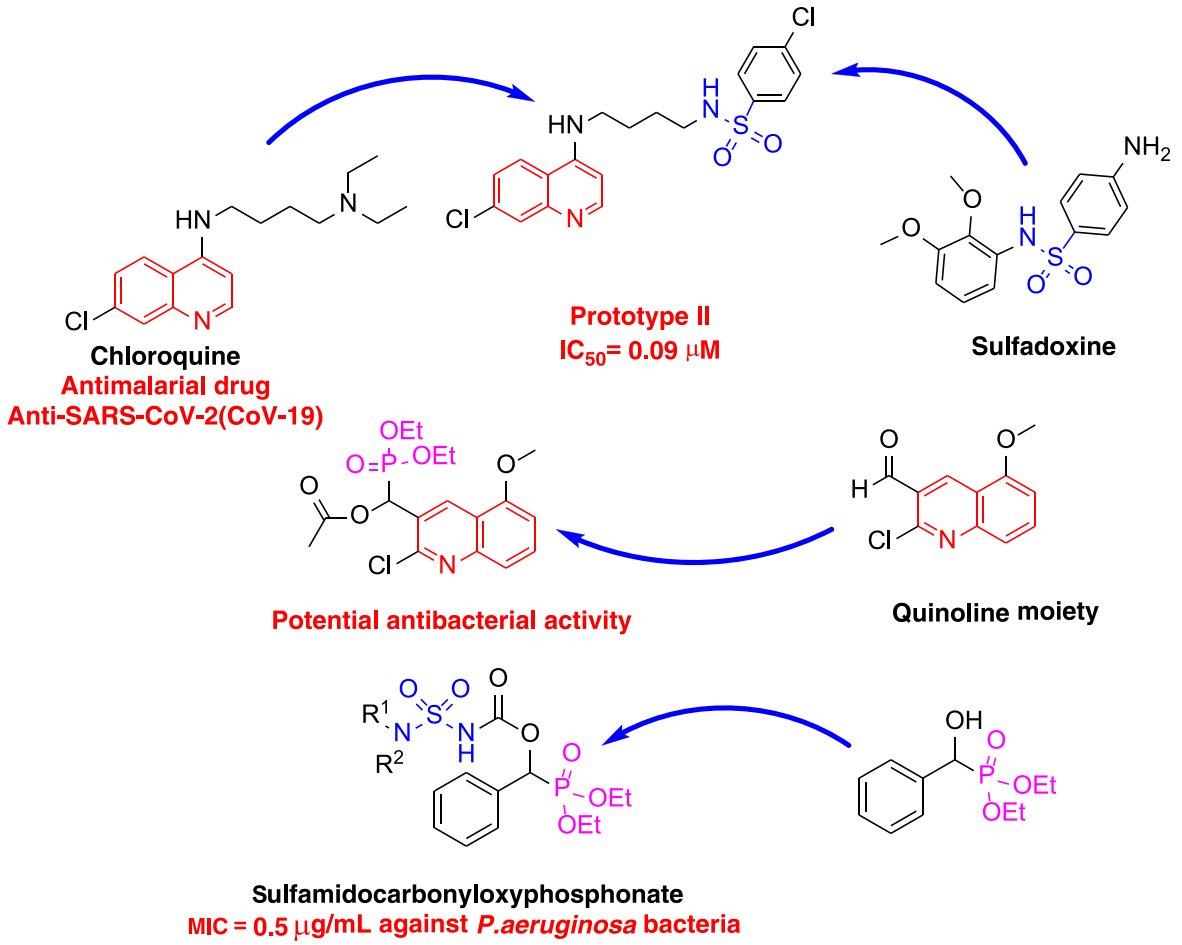


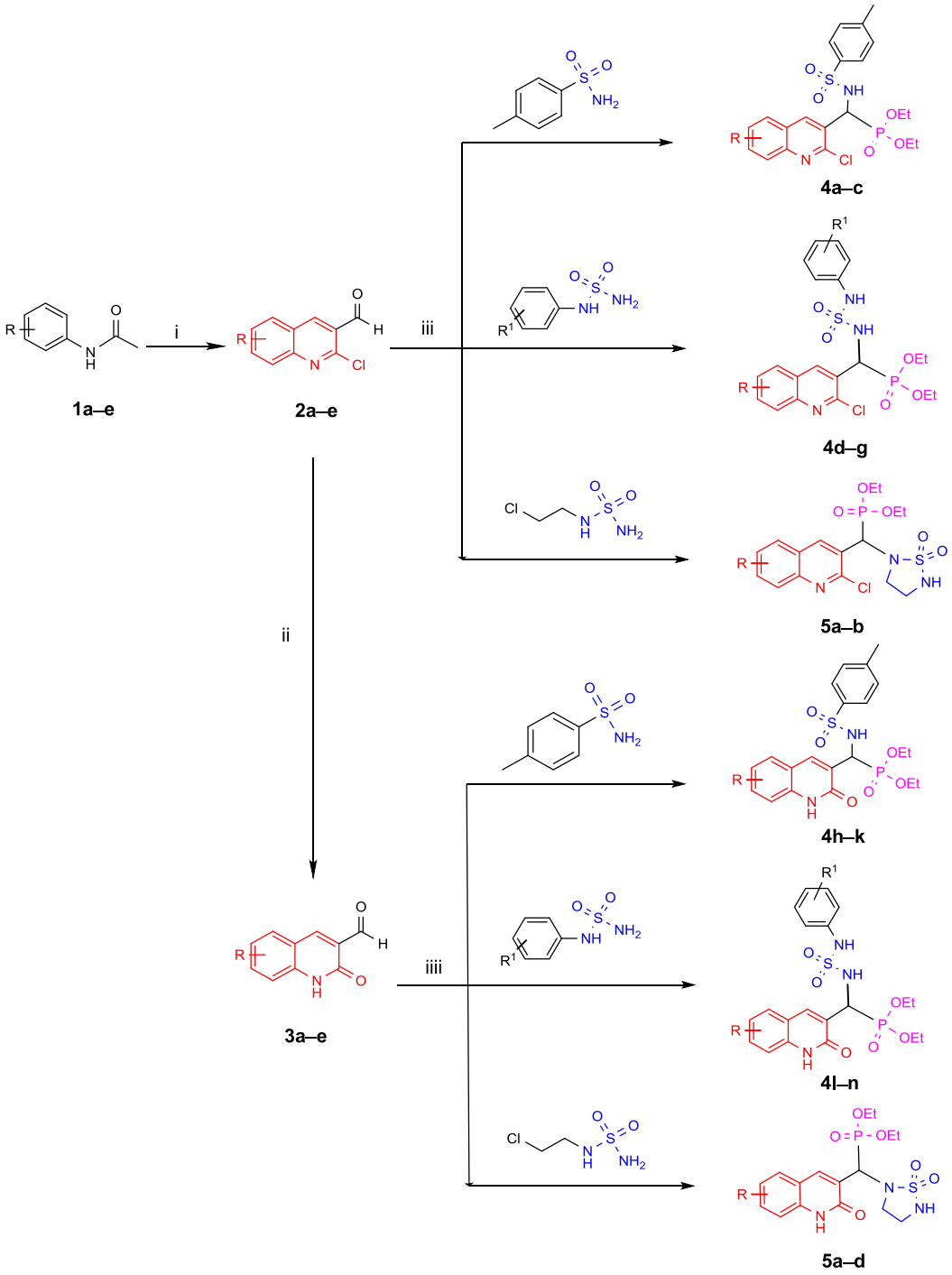
FIGURE 2 Rational approach to the design of active compounds containing sulfonamide/sulfamide, quinoline, and phosphonate moieties

previously reported by our research group[52] 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-sulfonamidophosphonate (**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 (^{1}H nuclear magnetic resonance [NMR], ^{13}C NMR, ^{31}P NMR, heteronuclear single-quantum coherence [HSQC], heteronuclear multiple bond correlation [HMBC], and elemental analysis).

The spectra ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, HSQC, and HMBC 2D NMR are available in the Supplementary Information Material; ^{1}H NMR spectra showed the characteristic signals of four principal types of protons in each product (OC**H**$_2$–C**H**$_3$, P–*C**H**N, N–**H** and Ar–**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_3 and CH_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*C**H**N between 4.9 and 5.6 ppm confirms the condensation of sulfonamide/sulfamide with the quinoline/quinolone carbaldehyde.

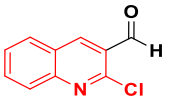
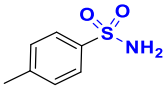
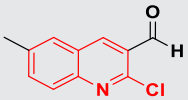
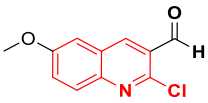
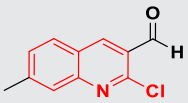
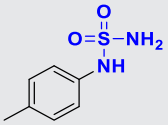
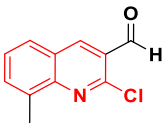
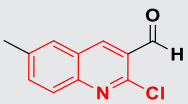
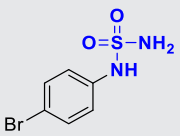
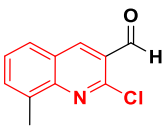
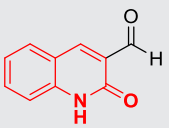
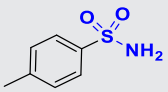
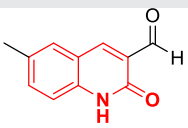
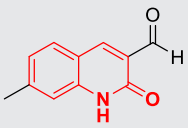
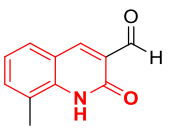
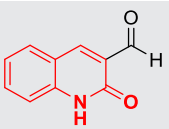
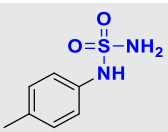


SCHEME 1 One-pot synthesis of novel α-sulfamidophosphonate/sulfonamidophosphonate and cyclosulfamidophosphonate derivatives under ultrasound irradiation

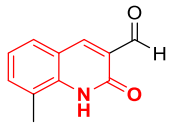
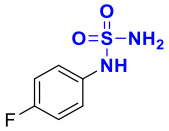
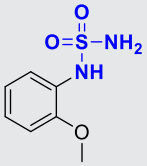
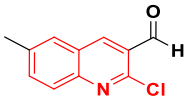
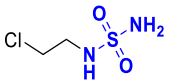
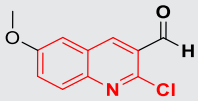
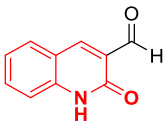
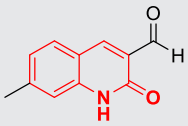
Since the peak of N–**H** protons appeared as two broad singlets, ranged between 3 and 11 ppm only for compounds **4d**–**g** and **4l**–**n**, which have two NH functions of sulfamide group (NH–SO_2–NH). Compounds **4a**–**c** and **4h**–**k**, on the contrary, have one NH function of sulfonamide group (NH–SO_2–R). While, the intramolecular cyclization and the formation of the cycle thiadiazolidine 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 2NC**H**$_2$ protons of the thiadiazolidine scaffold, according to the literature.[53] However, the last type of protons of aromatic rings is located between $\delta = 6.2$ and 8 ppm.

The ^{13}C 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

TABLE 1 Synthesis of novel α-sulfamidophosphonates/sulfonamidophosphonates (**4a–n**) and cyclosulfamidophosphonates (**5a–d**) under ultrasound irradiation[a]

Entry	Aldehyde	Sulfonamide/sulfamide	Time (min)	Yield (%)
4a			10	82
4b			13	79
4c			9	85
4d			8	88
4e			15	76
4f			14	87
4g			9	84
4h			7	90
4i			13	92
4j			10	78
4k			12	84
4l			8	95

(Continues)

Entry	Aldehyde	Sulfonamide/sulfamide	Time (min)	Yield (%)
4m			11	90
4n			14	86
5a			15	79
5b			16	75
5c			12	81
5d			14	86

Abbreviation: *IL*[TEAA], triethylammonium acetate.

[a]Conditions: aldehyde (1 mmol), amine (1 mmol), triethylphosphite (1 mmol), *IL*[TEAA], 40 kHz.

to the coupling of the carbon atoms with the phosphorus ($J_{C\text{-}P}$ 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 δ = 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 δ = 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 α-sulfamidophosphonates/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-quinoline 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 quinoline 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 α-aminophosphonates and sulfamides moieties mentioned above prompted us to test the antibacterial activities of the novel synthesized products. Hence, the

TABLE 2 Diameters of the inhibition zone (DIZ) of α-sulfonamidophosphonate/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.

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/sulfonamidophosphonate 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 25923) 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-sulfonamidophosphonate (**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 3 MICs and MBCs of sulfamidophosphonate/sulfonamidophosphonate (**4a–n**) and cyclosulfamidophosphonate (5a–**d**) derivatives

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

Abbreviations: MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; –, no inhibition (or concentration >512 μg/ml).
[a]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 sulfamethoxazole standard. The negative control (DMSO) did not show any antibacterial activity.

The results reveal that the compounds **4n**, **4f**, **4g**, **4m**, **4l**, **4d**, 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–SO_2–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–SO_2–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 quinoline 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 quinoline moiety, especially against Gram-negative bacterial strains.

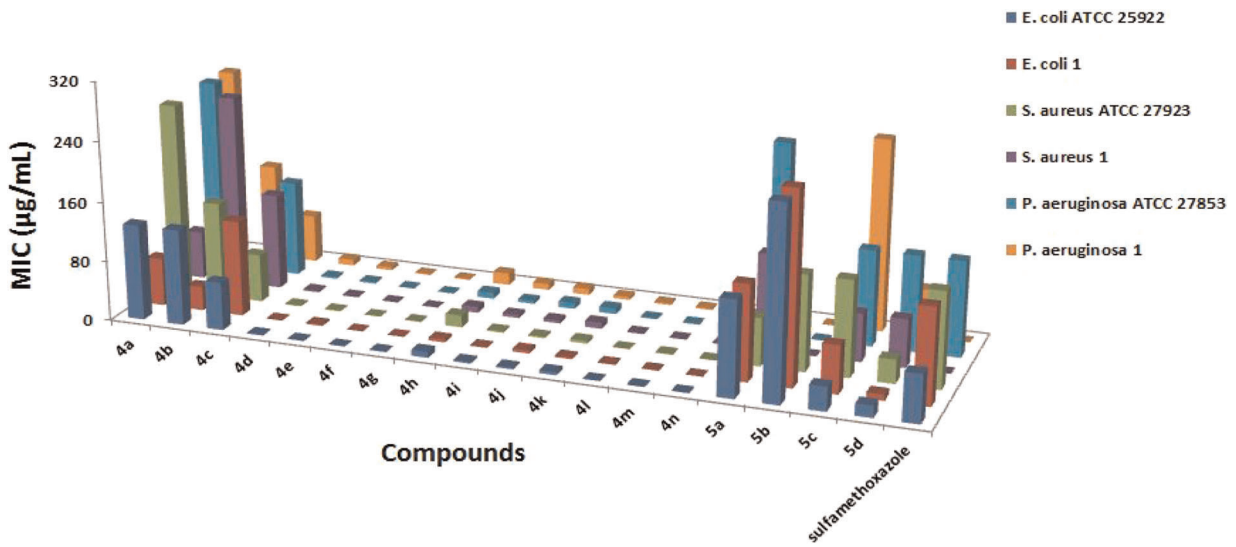


FIGURE 3 Comparison of antibacterial activity (minimum inhibitory concentration) of compounds **4a–n** and **5a–d** with sulfamethoxazole as reference

While the last series is the cyclosulfamidophosphonate derivatives **5a–d**, these compounds achieved good-to-moderate activity. The highest activity was shown against Gram-negative bacteria (*E. coli* and *S. aureus*) with DIZ values varied within 19 and 32 mm, and MIC values ranged between 8 and 128 µg/ml, only for compounds **5c** and **5d** that have a quinolone moiety. 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 quinolone 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**, **4l**, **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 oxyporum*. 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

TABLE 4 In vitro antifungal activity results of sulfamidophosphonate/sulfonamidophosphonate **4a–n**, cyclosulfamidophosphonate **5a–d** derivatives

Molecules	*Fusarium oxyporum* f. sp. *lycopersici*		*Alternaria* sp.	
	Percentage inhibition (%)[a]	MIC (μg/ml)	Percentage inhibition (%)[a]	MIC (μg/ml)
4a	78.14 ± 0.01	8	60.74 ± 0.09	16
4b	71.06 ± 0.25	4	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[b]	15 ± 0.10	256	38 ± 0.07	64

Abbreviation: MIC, minimum inhibitory concentration.
[a]Values are the means of three replicates ± *SD*.
[b]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 ranged 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 Merck silica gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and ninhydrin solution as developing agents. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25°C on Bruker spectrometers (400 MHz for ^{1}H, 101 MHz for ^{13}C, and 162 MHz for ^{31}P) using tetramethylsilane as internal standard and $CDCl_3$ or DMSO-d_6 as solvent. Elemental analysis (C, H, and N) were performed on a PerkinElmer 2400 CHN elemental analyzer model 1106. All reagents used for biological activities were purchased from Sigma-Aldrich Co.

The Supporting Information Data contains the ^{1}H, ^{13}C, ^{31}P NMR, HSQC, and HMBC 2D NMR spectra of all synthesized products and their spectral data.

4.1.2 | General procedure for the synthesis of sulfamide derivatives

The sulfamide derivatives were prepared starting from chlorosulfonyl isocyanate (CSI) in three steps (carbamoylation, sulfamolytion, and deprotection). To a stirred solution of CSI (1.62 g, 11.48 mmol) in 10 ml of anhydrous methylene chloride at 0°C was added 0.85 g, 11.48 mmol of *tert*-butanol in the same solvent. After a period of 30 min, the resulting solution and 1.75 ml, 1.1 eq of triethylamine was slowly added to a solution containing 1 eq of primary amine (aromatic amine or 2-chloroethylamine hydrochloride) in 10 ml of anhydrous methylene chloride at 0°C. The resulting reaction solution was allowed to warm up to room temperature for over 2 h. The reaction mixture was diluted with 30 ml of methylene chloride and washed with HCl (0.1 N) and then with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in a vacuum, to give carboxylsulfamides in excellent yields. The deprotection reaction of carboxylsulfamide was carried out in distilled water, the reaction mixture was refluxed for 15–30 min, and then it was extracted 3 × (30 ml) with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give sulfamides in good yields

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 ($POCl_3$; 7 eq) was added dropwise with stirring to it. To this solution, add acetanilide (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

$C_{11}H_8ClNO$; MW = 205.64; TLC R_f = 0.43 (CH_2Cl_2); yellow powder; mp: 176–177°C; 75% yield; IR ν_{max} (KBr) (cm^{-1}) = 1645 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H, CHO), 8.58 (s, 1HAr), 7.97 (d, J_{ortho} = 7.7 Hz, 1HAr), 7.75 (d, J_{metha} = 2.3 Hz, 1HAr), 7.74 (dd, J_{ortho} = 7.7, J_{metha} = 2.4 Hz, 1HAr), 2.57 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) 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**)*

$C_{11}H_9NO_2$; MW = 187.20; TLC R_f = 0.35 (CH_2Cl_2); yellow powder; mp: 205–206°C; 92% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H, NH), 10.24 (s, 1H, CHO), 8.40 (s, 1HAr), 7.71–7.65 (m, 1HAr), 7.49 (dd, J_{ortho} = 8.4, J_{metha} = 2.0 Hz, 1HAr), 7.27 (d, J_{ortho} = 8.4 Hz, 1HAr), 2.35 (s, 3H, CH_3-Ar) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): 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)sulfonamide]methyl}-phosphonate (**4a**)*

$C_{21}H_{24}ClN_2O_5PS$, MW = 482.92; TLC R_f = 0.51 (CH_2Cl_2/MeOH 7:3); white powder; mp: 162–163°C; 82% yield. ^{1}H NMR (400 MHz, chloroform-d_6) δ 11.82 (s, 1H, NH), 8.02 (d, J = 3.6 Hz, 1HAr), 7.83 (dd, J_{ortho} = 8.9, J_{metha} = 2.8 Hz, 2HAr), 7.66–7.53 (m, 1HAr), 7.60 (td, J_{ortho} = 8.8, J_{metha} = 2.3 Hz, 1H), 7.50 (td, J_{ortho} = 7.9, J_{metha} = 1.5 Hz, 1HAr), 7.38 (d, J = 8.3, 1HAr), 7.27 (s, 1HAr), 7.22 (td, J_{ortho} = 7.5, J_{metha} = 2.1 Hz, 1HAr), 7.15 (t, J = 7.3 Hz, 1HAr), 4.79 (d, $J_{H\text{-}P}$ = 26.8 Hz, 1H, P*CH), 4.34–4.15 (m, 2H, OCH_2CH_3), 3.13–2.84 (m, 2H, OCH_2CH_3), 2.40 (s, J = 7.3 Hz, 3H, CH_3–Ar), 1.32 (t,

J = 7.1 Hz, 3H, OCH_2CH_3), 1.22 (t, J = 7.2 Hz, 3H, OCH_2CH_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, $J_{C\text{-}P}$ = 2.7 Hz), 67.51 (d, $J_{C\text{-}P}$ = 161.6 Hz), 63.48 (d, $J_{C\text{-}P}$ = 7.0 Hz), 63.31 (d, $J_{C\text{-}P}$ = 7.2 Hz), 45.52, 21.47, 16.48 ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.10 ppm. Anal. calcd. for $C_{21}H_{24}ClN_2O_5PS$ (482.92): C, 52.23; H, 5.01; Cl, 7.34; N, 5.80; O, 16.57; P, 6.41; S, 6.64%; found: C, 52.41; H, 5.10; Cl, 7.30; N, 5.81; O, 16.62; P, 6.25; S, 6.48%.

*Diethyl((2-chloro-7-methylquinolin-3-yl){[N-(p-tolyl)sulfamoyl]amino}-methyl)phosphonate (**4d**)*

$C_{22}H_{27}ClN_3O_5PS$; MW = 511.96; TLC R_f = 0.66 (CH_2Cl_2/MeOH 7:3); yellow powder; mp: 170–171°C, 88% yield; ^1H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H, NH), 8.86 (dd, $J_{H\text{-}P}$ = 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_{metha} = 4.8 Hz, 1HAr), 7.42 (dd, J = 8.8, 1.7 Hz, 1HAr), 6.66 (d, J_{ortho} = 10.1 Hz, 2HAr), 6.51 (d, J = 10.1 Hz, 2HAr), 5.20 (dd, $J_{H\text{-}P}$ = 25.5, J = 11.5 Hz, 1H, P*CH), 4.18–3.58 (m, 4H, OCH_2CH_3), 2.03 (s, 3H, CH_3–Ar), 1.80 (s, 3H, CH_3–Ar), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.99 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.19, 146.79, 141.48, 141.35, 138.84, 135.63, 135.66, 131.25 (d, $J_{C\text{-}P}$ = 2.6 Hz), 128.91, 128.90, 127.51 (d, $J_{C\text{-}P}$ = 3.3 Hz), 124.81, 124.84, 124.87, 117.88, 117.85, 63.89, 63.09, 21.84, 20.32, 16.64 (d, $J_{C\text{-}P}$ = 8.8 Hz), 16.36 (d, J = 5.7 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 18.72 ppm. Anal. calcd. for $C_{22}H_{27}ClN_3O_5PS$ (511.96): C, 51.61; H, 5.32; Cl, 6.92; N, 8.21; O, 15.63; P, 6.05; S, 6.26%; found: C, 51.74; H, 5.45; Cl, 6.90; N, 8.26; O, 15.68; P, 6.07; S, 6.22%.

*Diethyl{[(4-methylphenyl)sulfonamide](2-oxo-1,2-dihydroquinolin-3-yl)methyl}phosphonate (**4h**)*

$C_{21}H_{25}N_2O_6PS$, MW = 464.47; TLC R_f = 0.51 (CH_2Cl_2/MeOH 7:3); white powder; mp: 190–191°C; 90% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H, NH), 8.05 (d, $J_{H\text{-}P}$ = 3.9 Hz, 1HAr), 7.73 (td, J_{ortho} = 7.5, 6.9, J_{metha} = 1.7 Hz, 2HAr), 7.50 (td, J_{ortho} = 8.3, 7.2, J_{metha} = 1.2 Hz, 2HAr), 7.36 (td, J_{ortho} = 8.4, J_{metha} = 2.1 Hz, 2HAr), 7.28 (d, J_{metha} = 2.3 Hz, 1HAr), 7.19 (td, J_{ortho} = 8.1, 7.4, J_{metha} = 1.2 Hz, 1HAr), 6.20 (dd, $J_{H\text{-}P}$ = 14.0, J = 6.2 Hz, 1H, NH), 5.33 (dd, $J_{H\text{-}P}$ = 13.4, J = 6.2 Hz, 1H), 4.40–3.99 (m, 4H, OCH_2CH_3), 2.37 (s, 3H, CH_3-Ar), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.17 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.15 (d, $J_{C\text{-}P}$ = 5.9 Hz), 142.28, 141.91, 138.47 (d, $J_{C\text{-}P}$ = 1.8 Hz), 138.02 (d, $J_{C\text{-}P}$ = 6.6 Hz), 131.17, 130.73, 129.72, 128.38, 126.09, 122.43, 119.47 (d, $J_{C\text{-}P}$ = 3.3 Hz), 115.39, 63.16 (d, $J_{C\text{-}P}$ = 165.4 Hz), 62.79 (d, $J_{C\text{-}P}$ = 6.6 Hz), 62.61 (d, $J_{C\text{-}P}$ = 7.0 Hz), 21.34, 16.81 (d, $J_{C\text{-}P}$ = 5.9 Hz), 16.72 (d, $J_{C\text{-}P}$ = 5.9 Hz) ppm. ^{31}P NMR (162 MHz, DMSO-d_6) δ 21.54 ppm. Anal. calcd. for $C_{21}H_{25}N_2O_6PS$ (264.12): C, 54.30; H, 5.43; N, 6.03; O, 20.67; P, 6.67; S, 6.90%; found: C, 54.35; H, 5.46; N, 6.01; O, 20.70; P, 6.65; S, 6.92%.

*Diethyl({[N-(4-fluorophenyl)sulfamoyl]amino}(8-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)phosphonate (**4m**)*

$C_{21}H_{25}FN_3O_6PS$; MW = 497.48; TLC R_f = 0.41 (CH_2Cl_2/MeOH 7:4); white powder; mp: 187–188°C; 90% yield. ^1H NMR (400 MHz, chloroform-d_6) δ 10.77 (s, 1H, NH), 8.05 (d, J = 3.9 Hz, 1HAr), 7.69 (d, J = 11.9 Hz), 7.45 (d, J_{ortho} = 7.5 Hz, 1HAr), 7.35 (d, J_{ortho} = 7.3 Hz, 2HAr), 7.28 (s, 1H, NH), 7.14 (t, J_{ortho} = 7.5 Hz, 1HAr), 6.93 (ddd, J_{ortho} = 9.3, 3.1, 1.6 Hz, 1HAr), 6.01 (s, 1H, NH), 5.40 (d, $J_{H\text{-}P}$ = 25.8 Hz, 1H, P*CH), 4.27–4.04 (m, 4H, OCH_2CH_3), 2.55 (s, 3H, CH_3–Ar), 1.35 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, chloroform-d_6) δ 175.49, 162.81 (d, $J_{C\text{-}P}$ = 4.4 Hz), 139.84 (d, $J_{C\text{-}P}$ = 7.3 Hz), 136.03 (d, $J_{C\text{-}P}$ = 1.8 Hz), 132.10, 127.22 (d, $J_{C\text{-}P}$ = 1.5 Hz), 126.41 (2CH), 123.76, 122.84 (2CH), 121.54 (d, $J_{C\text{-}P}$ = 7.7 Hz), 119.89 (d, $J_{C\text{-}P}$ = 2.9 Hz), 115.38, 115.16, 66.65 (d, $J_{C\text{-}P}$ = 161.4 Hz), 63.67 (d, $J_{C\text{-}P}$ = 5.9 Hz), 61.84 (d, $J_{C\text{-}P}$ = 5.5 Hz), 17.01, 16.28 (d, $J_{C\text{-}P}$ = 6.6 Hz), 16.09 (d, $J_{C\text{-}P}$ = 7.0 Hz). ^{31}P NMR (162 MHz, chloroform-d_6) δ 21.09 ppm. Anal. calcd. for $C_{21}H_{25}FN_3O_6PS$ (497.48): C, 50.70; H, 5.07; F, 3.82; N, 8.45; O, 19.30; P, 6.23; S, 6.44%; found: C, 50.77; H, 5.12; F, 3.81; N, 8.44; O, 19.34; P, 6.22; S, 6.43%.

*Diethyl[(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)(2-oxo-1,2-dihydroquinolin-3-yl)methyl] phosphonate (**5c**)*

$C_{16}H_{22}N_3O_6PS$, MW = 415,40; TLC R_f = 0.42 (CH_2Cl_2/MeOH 7:3); white powder; mp: 126–127°C; 81% yield. ^1H 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_{metha} = 2.2 Hz, 1HAr), 7.48 (ddd, J_{ortho} = 9.5, 7.7, J_{metha} = 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, $J_{H\text{-}P}$ = 12.6 Hz, 1H, P*CH), 4.34–4.04 (m, 4H, OCH_2CH_3), 2.04 (s, 4H, NCH_2–CH_2N), 1.30 (t, J = 7.5 Hz, 3H, OCH_2CH_3), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, chloroform-d_6) δ 163.18 (d, $J_{C\text{-}P}$ = 4.4 Hz), 139.25 (d, $J_{C\text{-}P}$ = 7.0 Hz), 137.56, 130.75, 128.20 (d, $J_{C\text{-}P}$ = 11.7 Hz), 127.68 (d, $J_{C\text{-}P}$ = 6.2 Hz) 123.02, 119.88 (d, $J_{C\text{-}P}$ = 2.9 Hz), 115.86, 66.20 (d, $J_{C\text{-}P}$ = 163.2 Hz), 63.54 (d, $J_{C\text{-}P}$ = 7.0 Hz), 63.42 (d, $J_{C\text{-}P}$ = 7.3 Hz), 45.17, 21.91, 16.43, 16.37 ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.35 ppm. Anal. calcd. for $C_{16}H_{22}N_3O_6PS$ (415.40): C, 46.26; H, 5.34; N, 10.12; O, 23.11; P, 7.46; S, 7.72%; 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.[57] 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 negative control contains the PDA and DMSO without any other products. Experimentally, a disk of 5 mm in diameter is taken from a young fungal culture and is deposited in the center of the Petri dish containing the PDA medium and the tested compound. 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 % = $(C - T/C) \times 100$, where C is the colony diameter of the 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.

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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SUPPORTING INFORMATION

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