MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and potential antimicrobial activity of novel α-aminophosphonates derivatives bearing substituted quinoline or quinolone and thiazole moieties

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Abstract

To develop novel antimicrobial agents, and based on the biologically active heterocyclic quinoline and thiazole substituted, a series of novel α-aminophosphonates (**9a–h**) and (**10i–l**) derivatives that incorporated quinoline or quinolone, and coumarylthiazole or 5-phenylthiazol-2-amine moieties were designed and synthesized via Kabachnik–Fields reaction in the presence of ionic liquid under ultrasound irradiation. All the new compounds were obtained in good yield with a simple workup and were confirmed using various spectroscopic methods. The in vitro antimicrobial activity of all synthesized compounds were screened in terms of MIC values against the selected strains of Gram-negative and Gram-positive bacteria and two fungal strains using the broth micro-dilution method. The results showed that most of the tested compounds showed moderate inhibitory activities against both Gram-positive and -negative bacteria compared with reference drugs. The following compounds **9e**, **9g**, **9h**, **9i** and **9f**, **9g**, **9h**, **10k**, **10l** are the most active against Gram-positive and Gram-negative bacteria strains, respectively, with MIC values ranging between 0.25 and 128 μg/mL. The synthesized compounds **9b**, **9c**, **9f**, **9g**, **9h**, **10k**, and **10l** exhibited excellent antifungal inhibition with MIC values ranging between 0.25 and 32 μg/mL. Structure–activity relationship revealed that the presence of coumarylthiazole moiety and hydroxyl in the quinoline group increased the inhibitory activity against microbial strains pathogens. These results confirm that the synthesized compounds can be potential antimicrobial drugs candidate.
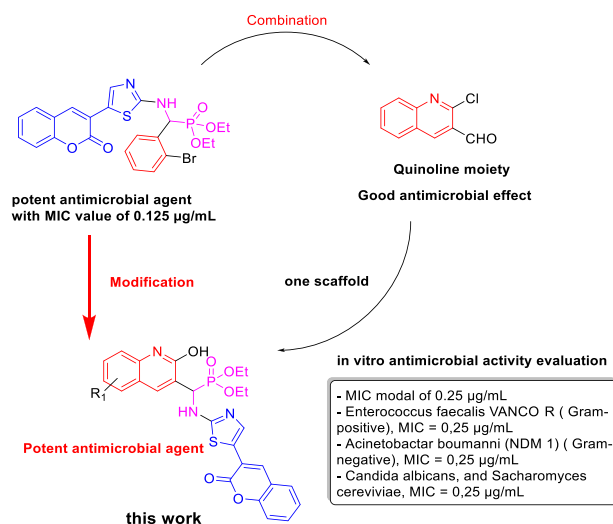
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Graphical Abstract

Introduction

According to the World Health Organization (WHO), bacterial infections are among the top ten causes of morbidity and mortality worldwide [1]. Data from the WHO have revealed that more than 2 million infections with a death toll of 29,000 occurring in the US per annum are directly related to bacterial infections, and cost more than $4.7 billion [2, 3]. Although there are many antimicrobial drugs currently in use in clinical medicine, they become less effective in a short time because microorganisms rapidly develop resistance mechanisms [4]. Based on these facts, the discovery of new and effective drugs must be discovered to overcome bacterial resistance and develop effective treatments [5].
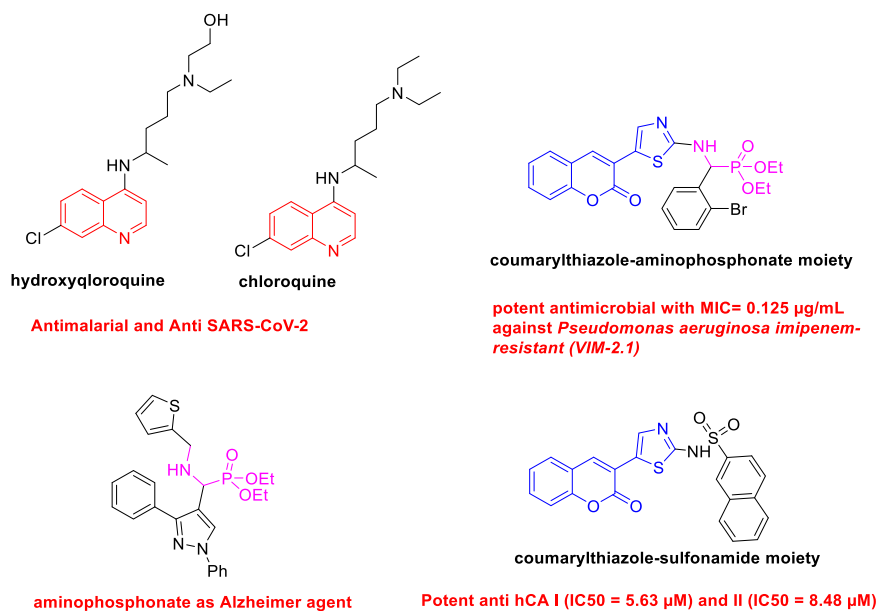
Quinoline belongs to a biologically active class of compounds as they show quite diverse biological activities [6]. Many scientific reports revealed that natural and synthetic quinolines are drawn considerable attention in medicinal chemistry [7, 8]. The great attention paid by researchers to the study of quinoline derivatives is explained by their broad range of biological activities, such as anti-Alzheimer [9], antidiabetic [10], anti-inflammatory [11], antituberculosis [12], anticancer [13], antioxidant [14], and as inhibitors of SARS-CoV-2 (COVID-19) virus [15–17]. Therefore, compounds containing thiazole heterocycles are well known in medicinal chemistry [18], thiazole derivatives exhibit significant biological activities, such as antimicrobial and antimalarial [19], Alzheimer [20], antiproliferative agents [21], anticancer agents [22], and anti-inflammatory [23]. In addition, coumarins are an important class of heterocyclic compounds with various biological activities [24]. The combination of coumarin and a thiazole ring is of great significance in pharmaceutical chemistry. Coumarin–thiazole compounds have shown many biological activities such as anti-acetylcholinesterase [25], anti-inflammatory [26], antibacterial and antituberculosis agents [27], antioxidant, and inhibition of carbonic anhydrase [28, 29] (Fig. 1).

Recently, α-aminophosphonates have received enormous attention from scientific researchers in pharmaceutical and medicinal chemistry [30], due to structural analogies to amino acids and exhibit many biological properties [31], such as anti-Alzheimer [32], antimicrobial [33], antiviral [34], and antioxidant [35]. The Kabachnik–Fields reaction is one and the simplest of the most practical approaches for α-aminophosphonate syntheses; the reaction generally requires various catalysts, such as CF_3CO_2H [36], TiO_2 [37], Amberlite-IR 120 [38], $SnCl_2$ [39], phenyl phosphonic acid [40], and ethyl lactate [41]. However, many of these catalysts are expensive and have to be used in stoichiometric amounts. The green catalyst synthesis of α-aminophosphonates is rather limited [42].

Based on these facts and keeping in view the wide range of biological activities of quinoline or quinolone, thiazole moieties, and aminophosphonate scaffolds, in this work, we expect that the incorporation of all these moieties in the same scaffold structure may lead to good activities and potent antibacterial agents. Thus, we have designed and synthesized a series of novel α-aminophosphonates derivatives bearing quinoline or quinolone rings, and thiazole moieties were evaluated against references and multidrug-resistant bacteria and fungal strain.

hydroxyqloroquine

chloroquine

Antimalarial and Anti SARS-CoV-2

coumarylthiazole-aminophosphonate moiety

potent antimicrobial with MIC= 0.125 µg/mL against *Pseudomonas aeruginosa imipenem-resistant (VIM-2.1)*

aminophosphonate as Alzheimer agent

coumarylthiazole-sulfonamide moiety

Potent anti hCA I (IC50 = 5.63 µM) and II (IC50 = 8.48 µM)

Results and discussions

Chemistry

Two series of 12 novel α-aminophosphonate (**9a–h**) and (**10i–l**) derivatives that incorporated quinoline or quinolone, and coumarylthiazole or 5-phenylthiazol-2-amine moieties were designed and synthesized by condensation of three components via one-pot Kabachnik–Fields reaction under ultrasound (US) irradiation. Our design strategy was based on the synthesis of novel α-aminophosphonates moiety containing quinoline or quinolone scaffold to improving the biological activity against microbial strains.

The synthesis of all intermediates and target molecules was performed according to the reactions outlined in Schemes 1–3. The first step of the synthesis involved formation of aldehyde derivatives (quinoline and quinolone) and functionalized 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (**3**) and 5-phenylthiazol-2-amine (**5**). The reaction to give the target compound (**9a–h**) and (**10i–l**) derivatives was started from 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (**3**) or 5-phenylthiazol-2-amine (**5**), respectively, quinoline/quinolone carbaldehyde, and triethylphosphite under US irradiation using ionic liquid triethylammonium acetate [TEAA] as a catalyst at room temperature (Scheme 3).

The 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (**3**) and 5-phenylthiazol-2-amine (**5**) presented in this study were obtained from a simple and efficient methodology described in the literature [43] as shown in Scheme 1. At first, 3-acetylcoumarin (**1**) was obtained by the condensation between salicylaldehyde and ethyl acetoacetate in ethanol at 0–5 °C in the presence of a catalytic amounts of piperidine. The second precursors, 3-(2-bromoacetyl)-2H-chromen-2-
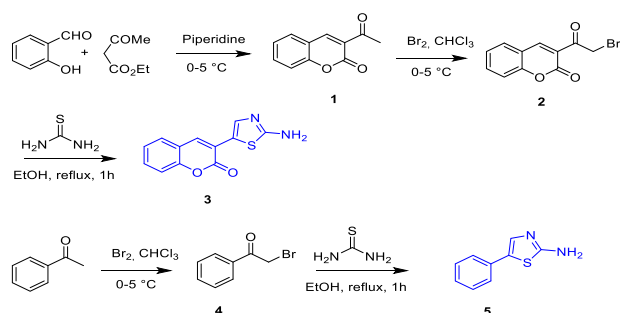

Scheme 1 Synthesis of 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (**3**) and 5-phenylthiazol-2-amine (**5**)
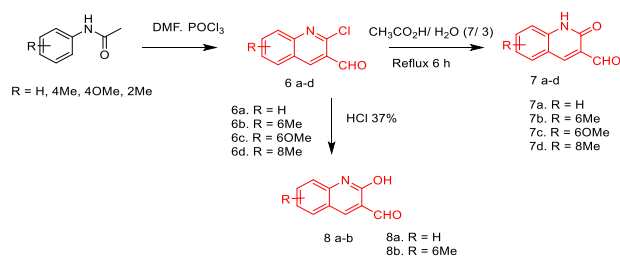
Scheme 2 Synthesis of quinoline and quinolone derivatives

one (**2**) and 2-bromo-1-phenylethan-1-one (**4**), were synthesized by brominating 3-acetylcoumarin and acetophenone respectively in chloroform. 3-(2-Aminothiazol-5-yl)-2H-chromen-2-one (**3**) and 5-phenylthiazol-2-amine (**5**) were obtained by reaction of compounds (**2**) and (**4**) with thiourea in ethanol and neutralized with ammonia. 2-Chloroquinoline-3-carbaldehyde derivatives (**6a–d**) were obtained via Meth–Cohn reaction [44], which included the condensation of acetanilide derivatives with Vilsmeier–Haack

Scheme 3 Synthesis of new α-aminophosphonate quinolone/quinolone thiazole derivatives: (i) aldehyde (1 mmol), amine (1 mmol), triethylphosphite (TEP) (1 mmol), ILs (TEAA) (1 mL), US (40 kHz), rt
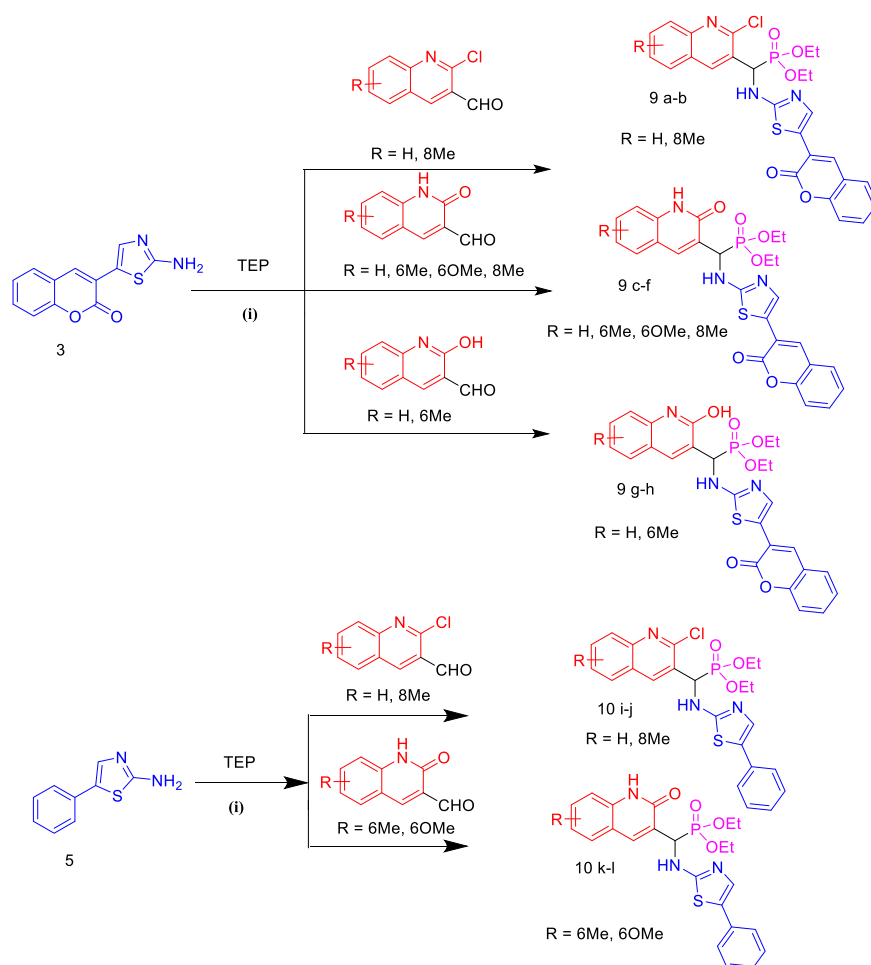
reagent. 2-Oxoquinoline-3-carbaldehyde derivatives (**7a–d**) were then obtained by the hydrolytic reaction of compounds (**6a–d**) in the presence of 70% acetic acid [45]. As a continuation, compounds (**8a–b**) were obtained when treating 2-chloro-quinoline-3-carbaldehyde derivatives in the presence of Clorohydric acid (HCl 37%) [46]. The TEAA has been easily prepared from the reaction of triethylamine and acetic acid (CH₃CO₂H) according to the reported method [47], and was found in excellent yield 98%.

Finally, compounds (**9a–h**) and (**10i–l**) were obtained when compounds (**3**) and (**5**) were reacted with an aldehyde (quinoline or quinolone derivatives), and triethylphosphite via one-pot Kabachnik–Fields reaction under US irradiation in the presence of ionic liquid [TEAA] as a catalyst (Scheme 3).

In continuation of our previous research project [48, 49] toward the development and synthesis of novel biomolecule compounds contain α-aminophosphonate moiety in high yields and clean conditions, in this study, we reported and used our previous strategy for the synthesis of new α-aminophosphonate (**9a–h**) and (**10i–l**) derivatives using the ionic liquid [TEAA] under US irradiation. We have found that the ionic liquid [TEAA] presented several advantages

for the synthesis of α-aminophosphonate derivatives, such as giving pure product without chromatography purification and excellent yield in short reaction time with a simple workup.

All the new compounds (**9a–h**) and (**10i–l**) were characterized and confirmed by spectroscopic techniques infrared [IR], 1H-nuclear magnetic resonance [^{1}H-NMR], ^{13}C-NMR, ^{31}P-NMR, and 2D NMR heteronuclear single-quantum coherence [HSQC], heteronuclear multiple bond correlation [HMBC], and elemental analysis. These techniques helped for determining and confirm the molecular structures of the synthesized compounds (Table 1).

From the ^{1}H-NMR spectroscopic, it was possible to observe the presence of principal signals of protons in each product. The lack of the signal of the aldehyde confirmed the structure of synthetized compounds, the proton (N-H) of α-aminophosphonates groups was detected between $\delta = 9$ and 12 ppm, the signals at $\delta = 1.20$ and 4.20 ppm corresponded to methylene (**CH₃**-CH₂-O) and ethylene (CH₃-**CH₂**-O) respectively of phosphonates groups, the proton of asymmetric carbone (P*CH) is clearly detected between $\delta = 5.90$ and 6.20 ppm, the signals at $\delta = 7.50$ ppm

Table 1 Synthesis of novel α-aminophosphonate (9a–h) and (10i–l) derivatives under ultrasound irradiation in ionic liquid TEAA
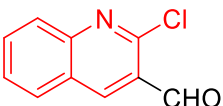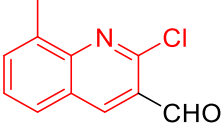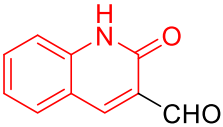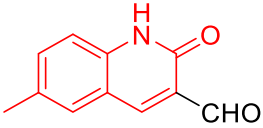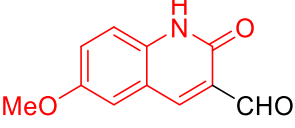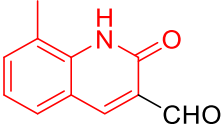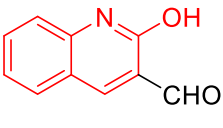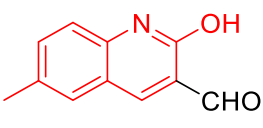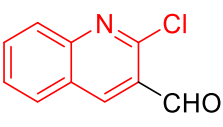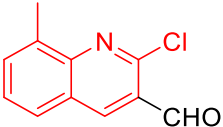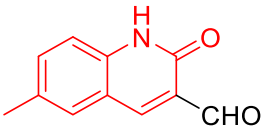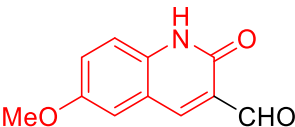
Entry	Aldehyde (quinoline/quinolone)	Thiazole derivatives	Time (min)	Yield (%)[a]	m.p. (°C)
9a			17	73	237–238
9b			22	70	130–132
9c			15	86	204–205
9d			13	84	275–276
9e			10	83	242–244
9f			16	85	152–154
9g			23	78	173–177
9h			19	71	209–210
10i			14	88	201–203
10j			16	84	131–132

Table 1 (continued)

Entry	Aldehyde (quinoline/quinolone)	Thiazole derivatives	Time (min)	Yield (%)[a]	m.p. (°C)
10k			14	90	272–274
10l			18	89	138–139

Conditions: aldehyde (quinoline/quinolone) (1 mmol), amine (1 mmol), triethylphosphite (1 mmol), ILs (triethylammonium acetate) (1 mL), 40 kHz

[a]Yield (%): a yield of isolated product

corresponded to the protons of thiazole rings. For compounds (**9a–h**), we detected that signals at $\delta = 8.50$ ppm corresponded to coumarin rings, compounds containing quinolone and 2-hydroxyquinoline moiety showed that the signals at $\delta = 11.98$ and 11.80 ppm corresponded for (N-**H**) and (O-**H**) hydroxyl groups of quinolone and 2-hydroxyquinoline moiety, respectively. However, for all synthesized compounds the last type of protons of aromatic rings is located between $\delta = 7.4$ and 8.45 ppm. The ^{13}C-NMR spectroscopic analysis of all new compounds also confirmed that structural identity by observing the new characteristic type of doublets signals at $\delta = 16.50$ and 63.20 ppm corresponded for methylene (**CH$_3$**-CH$_2$-O-**P**) and ethylene (CH$_3$-**CH$_2$**-O-**P**) respec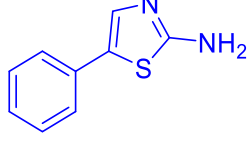tively due to the coupling of the carbon atoms with the phosphorus atoms (**J$_{C-P}$**), the peak corresponded the asymmetric carbone (P***CH**) was observed at $\delta = 46$ ppm, the peaks corresponded to coumarin lactone and thiazole ring detected at $\delta = 138$ and 142 ppm, respectively. However, compounds containing quinolone moiety showed a peak relating to the carbonyl of the amide group (HN–**C** = O) at $\delta = 160$ ppm.

In the ^{31}P-NMR spectrum, the phosphorus atom was resonated as a single ranging between $\delta = 19$ and 21.2 ppm approximately in all the synthesized compounds.

The structures of the representative compounds were confirmed by 2D NMR, HSQC, and HMBC. The HSQC spectra confirm the vicinal relationship (C–H correlation 1–2) and the HMBC spectra mode indicates the C–H correlation 1–3. The elemental analysis furthermore confirmed the assigned structures of all synthesized compounds.

Antimicrobial activity

In medicinal chemistry, the combinations of two or more pharmacophores into one scaffold are a common procedure for the discovery and development of new drugs.

Recently, quinolones/quinolones and thiazole derivatives are known for their strong antimicrobial effect and displayed good antibacterial activity [50, 51]. In contrast, the literature reports reveal that the α-aminophosphonates derivatives displayed good and promising antimicrobial activity [49].

To identify new antimicrobial agents, our combination strategy was based on the synthesis of new α-aminophosphonates containing quinoline or quinolone derivatives substituted with coumarylthiazole/5-phenylthiazole in the same scaffold. Moreover, we expected that the presence of α-aminophosphonates moiety contributes to improving the antimicrobial activity against references, multidrug-resistant bacteria, and fungal strains.

The antimicrobial profile of the newly synthesized compounds (**9a–h**) and (**10i–l**) have been evaluated in vitro for their antibacterial activity against the selected strains of Gram-negative and Gram-positive bacteria and two fungal strains, using the broth micro-dilution method. Dimethyl sulfoxide (DMSO) was used as a negative control. For the control test, we have used Imipenem, Ciprofloxacin, Amikacin, and Fluconazole as a positive control to compare the minimal inhibitory concentration (MIC). The MIC values are reported in Tables 2 and 3.

The results reveal that all compounds have shown excellent antimicrobial effects against both Gram-negative and Gram-positive bacteria strains compared with standard drugs (positive control). In case of a Gram-positive bacterial study, the MIC values listed in Table 2 revealed that the synthesized compounds (**9a–h**) and (**10i–l**) had promising antimicrobial profiles against *Enterococcus faecalis* ATCC 29212, vancomycin-resistant *Enterococcus faecalis* with MIC values ranging between 0.25 and 32 μg/mL. Compound **9g** was found to be the most potent one against *Bacillus cereus*, *Staphylococcus aureus* resistant to ciprofloxacin, *Enterococcus faecalis* ATCC 29212, vancomycin-

Table 2 MICs (µg/mL) values of the synthesized α-aminophosphonates (9a–h) and (10i–l) derivatives against the tested Gram-positive bacteria

Compounds	Bacillus cereus	Staph. aureus cip R	Staph. aureus ATCC 25923	Staph. aureus ATCC 6538	Enterococcus faecalis VANCO R	Enterococcus faecalis ATCC 29212
9a	2	512	512	128	0.5	0.5
9b	256	256	256	128	0.5	2
9c	32	64	0.25	++	1	++
9d	++	64	64	++	0.25	++
9e	32	32	++	++	0.5	0.5
9f	++	++	++	++	0.25	0.5
9g	2	0.5	++	++	0.25	0.5
9h	4	32	128	++	0.5	0.5
10i	++	0.5	0.5	1	1	32
10j	128	8	++	++	++	1
10k	2	256	256	++	1	0.5
10l	16	++	++	++	0.5	2
Imipenem[a]	–	–	–	–	–	–
Ciprofloxacin[a]	–	–	–	–	–	–
Amikacine[a]	–	–	–	–	–	–
Fluconazole[a]	–	–	–	–	–	–

++: no inhibition (or concentration >512 µg/mL), –: not applicable

[a]Positive reference, *R* resistant, *MIC* minimum inhibitory concentration

resistant *Enterococcus faecalis* with MIC values ranging between 0.25 and 2 µg/mL followed by compounds **9e**, **9h**, and **10i** with MIC values between 0.25 and 128 µg/mL while other derivatives are moderately active. On the other hand, bacteria strains *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* ATCC 6538 exhibited less resistance against the synthesized compounds and the MIC values ranging between 0.25 and 512 µg/mL.

In case of Gram-negative bacterial study, the MIC values listed in Table 3 revealed that all the newly synthesized compounds (**9a–h**) and (**10i–l**) exhibited broad-spectrum activity with excellent and high inhibition against all Gram-negative bacteria with MIC modal of 0.25 µg/mL. Most of the synthesized compounds have exhibited moderate and high inhibition against *Escherichia coli* ESBL (enlarged specter β-lactamase) producer, *Escherichia coli* resistant to ciprofloxacin, *Pseudomonas aeruginosa* imipenem-resistant (VIM-2), *Acinetobacter baumanni* (NDM-1), *Pseudomonas aeruginosa* ATCC 9027, *Enterobacter cloacae* fosfomycin resistant, *Klebsiella pneumoniae* Carbapenem-resistant (KpC +), *Klebsiella pneumoniae* Carbapenem-sensitive (KpC–), *Serratia marcescens* with MIC values ranging between 0.25 and 128 µg/mL. Particularly, the results reveal that the compounds **9f**, **9g**, **9h**, and **9e** have shown the highest antibacterial activity and excellent inhibition from compounds bearing coumarylthiazole moiety (**9a–h**) and compounds **10k** and **10l** from compounds bearing 5-phenylthiazole moiety (**10i–l**) against *Escherichia coli* resistant to ciprofloxacin, *Pseudomonas aeruginosa* imipenem-resistant (VIM-2), *Acinetobacter*

baumanni (NDM-1), *Enterobacter cloacae* fosfomycin resistant, *Escherichia coli* ESBL producer, *Serratia marcescens* bacteria strains with MIC values ranging between 0.25 and 64 µg/mL and even more efficient than the standard drugs Imipenem, Ciprofloxacin, and Amikacine. So most of these compounds can be considered as broad-spectrum potential antibacterial agents.

From the results of Table 3, we have found two MIC values (MIC = 0.25/32 µg/mL) for compound **9a** against *Salmonella typhi* and two MIC values (MIC = 0.5/64 µg/mL) for compound **9g** against *E. Coli* ESBL producer. These results are explained by the compatibility between the permeability of the bacterial membrane and the concentration of the compound.

The in vitro antifungal activity of all the synthesized compounds (**9a–h**) and (**10i–l**) was screened against two fungal strains *Candida albicans* and *Saccharomyces cerviceae* using the drug Fluconazole as a reference standard (positive control). The results listed in Table 4 clearly showed that all the tested compounds had excellent antifungal effects against the different fungal strains ranging between 0.25 and 32 µg/mL. The highest activity was observed with the compounds **9b**, **9c**, **9f**, **9g**, **9h** and **10k**, **10l** from compounds bearing both coumarylthiazole moiety (**9a–h**) and 5-phenylthiazole moiety (**10i–l**), respectively, with MIC ranging between 0.25 and 32 µg/mL less and much better than the drug fluconazole 2 µg/mL, and based on these facts we can consider most of the synthesized compounds as potential antifungal agents candidates.

Table 3 MICs (µg/mL) values of the synthesized α-aminophosphonates (9a–h) and (10i–l) derivatives against the tested Gram-negative bacteria

Compounds	E. coli ATC-C 25922	E. coli ESBL	E. coli cipro R	Pseudomonas aeruginosa (VIM-2)	Acinetobacter baumanni (NDM-1)	Acinetobacter baumanni OXA-23	Pseudomonas aeruginosa ATCC 9027	Enterobacter cloacoe fos R	KpC +	KpC -	E. coli mc-r-1	E. coli ESBL producer	E.coli ATC-C 8739	Serratia marcescens	Salmonella typh-i 14028	Citrobacter sp
9a	2/32	2	64	0.5	256	++	256	128	1	16	1	64	64	++	0.25/32	1
9b	1	256	64	32	++	1	1	0.5	1	65	256	1	64	1	1	256
9c	0.5	++	256	0.25	16	4	16	0.5	256	256	++	++	4	1/64	16	++
9d	2	4	8	0.25	256	++	1	4	2	++	32	256	++	0.5	++	8
9e	++	128	0.5	0.25	8	++	0.25	8	16	1	128	1	0.25	8	++	2
9f	++	2	128	1	0.25	++	++	0.25	++	128	++	0.25	++	0.25	0.25	0.25
9g	1	0.25	32	0.5	0.25	2	++	0.5	1	2	++	0.5/64	++	0.5	64	++
9h	8	32	32	0.25	0.25	32	32	64	32	++	32	32	++	32	32	64
10i	++	++	++	0.25	128	++	++	32	++	0.25	++	4	++	0.25	++	++
10j	++	++	++	0.5	0.5	++	1	0.25	++	1	++	0.25	++	32	++	++
10k	++	++	0.5	1	0.5	++	8	0.5	0.25	0.5	++	0.5	32	8	++	0.5
10l	32	16	0.5	0.5	0.5	16	8	0.5	1	1	0.5	++	0.5	0.25	++	32

It is important to highlight that the synthesized compounds (9a–h) and (10i–l) showed promising antimicrobial effects against pathogenic Gram-positive and Gram-negative and fungi strains. The results from these studies and based on the results of Tables 2 and 3, we found that the quinoline-α-aminophosphonate derivatives substituted with coumarylthiazole/5-phenylthiazole play an important role in the antimicrobial activity.

In this study, we found that the presence of quinoline-α-aminophosphonate moiety in the same scaffold with coumarylthiazole/5-phenylthiazole group significantly increases the antibacterial activity with interest and promise MIC values relatively low and much lower than the MIC of antibiotics used in medicine: Imipenem, Ciprofloxacin, Amikacine, and Fluconazole (Fig. 2). All the newly synthesized compounds (9a–h) and (10i–l) showed a modal MIC around 0.25 µg/mL and exhibited a broad spectrum of antimicrobial activity.

Structure–activity relationship analysis

From the in vitro antibacterial and antifungal results, the structure–activity relationship (SAR) of synthesized quinoline-aminophosphonate molecules can be derived (Fig. 3).

The following SAR observations can be drawn from data of Tables 2 and 3. In general, compounds bearing coumarylthiazole group (9a–h) possessed much higher activity against Gram-negative and Gram-positive bacteria pathogen strains than those containing 5-phenylthiazole group (10i–l) that showed less activity against Gram-positive strains. However, the newly synthesized α-aminophosphonates derivatives bearing 2-hydroxyquinoline and quinolone moiety were the most active and demonstrated a high antibacterial activity compared with those bearing 2-chloroquinoline moiety.

(i) The best inhibitor among the synthesized and investigated compounds was the α-aminophosphonates derivatives bearing 2-hydroxyquinoline and coumarylthiazole group 9g and 9h against microbial pathogen strains. These results showed a qualitative relationship between the presence of 2-hydroxyquinoline and coumarylthiazole group in the same scaffold with MIC values ranging between 0.25 and 128 µg/mL.

(ii) For quinolone derivatives, compounds containing quinolone and coumarylthiazole/5-phenylthiazole in the same scaffold 9e, 9f, and 10k, 10l showed interesting effects against both bacterial and fungal strains with moderate MIC values ranging between 0.25 and 128 µg/mL and more active than compounds bearing quinoline moiety that showed less antimicrobial activity.

**Table 4** In vitro antifungal activity results of the synthesized α-aminophosphonates (9a–h) and (10i–l)

Compounds	Candida albicans	Saccharomyces ceriviceae
9a	8	32
9b	2	1
9c	0.25	0.5
9d	0.25	32
9e	1	32
9f	1	0.5
9g	0.5	1
9h	0.5	1
10i	++	8
10j	0.5	32
10k	32	2
10l	1	0.5
Fluconazole[a]	2	–

++: no inhibition (or concentration >512 µg/mL), –: not applicable

[a]Positive reference, *R* resistant, *MIC* minimum inhibitory concentration
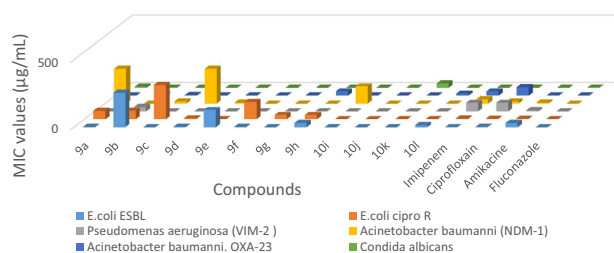
Fig. 2 Comparison of MIC values of quinoline-aminophosphonate derivatives (**9a–h**) and (**10i–l**) with standard drugs: Imipenem, Ciprofloxacin, Amikacine, and Fluconazole as reference

According to the SAR study, it is clear that the inhibitory effect is directly related to the type of the substituted group on α-aminophosphonates moiety. The presence of quinolone and 2-hydroxyquinoline moiety can increase the inhibitory effect against microbial strains. These results confirm that the bulky substituted coumarylthiazole moiety is still more active against both references and MDR and fungal strains than 5-phenylthiazole moiety.

Conclusion

In this study, we designed, synthesized, and evaluated a series of novel scaffolds of quinoline/thiazole-derived α-aminophosphonates for their antimicrobial activity. Among the tested compounds, compounds **9e**, **9g**, **9h**, **9i** and **9f**, **9g**, **9h**, **10k**, **10l** showed better antibacterial inhibitory activity against Gram-positive and Gram-negative bacteria strains, respectively, compared to the standard drugs Imipenem, Ciprofloxacin, Amikacine with MIC values ranging between 0.25 and 128 µg/mL. Compounds **9b**, **9c**, **9f**, **9g**, **9h, 10k**, and **10l** were the most potent derivatives with MIC values ranging from 0.25 to 32 µg/mL against the two tested fungal strains compared to the standard drug fluconazole. According to the SAR analysis, the inhibitory activity of the synthesized compounds could also be affected by the type of substituent. The presence of coumarylthiazole moiety, and hydroxyl in the quinoline group increased the inhibitory activity against all tested microbial strains pathogens. It can be concluded that most of the synthesized compounds showed potent antimicrobial activities against the tested pathogenic strains. Subsequently, these results can help researchers to look for new potent antimicrobial agents for therapeutic use.
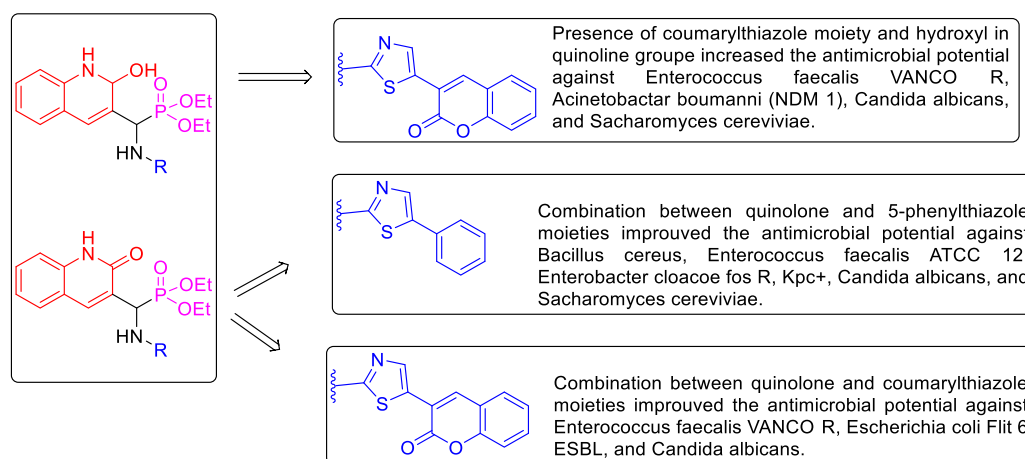
Fig. 3 Structural requirements for the antimicrobial activity of synthesized quinoline-aminophosphonate derivatives (**9a–h**) and (**10i–l**)

Experimental section

General

All chemicals reagents used for synthesis were obtained from commercial sources and purchased from Merck, Sigma-Aldrich, and Fluka and were used without purification. Melting points (m.p.) of the synthesized compounds were taken by the Buchi Melting Point B-545 apparatus and the values are uncorrected. US irradiation was performed in a FUNGILAB ultrasonic bath with a frequency of 40 kHz and output power of 250 W. IR spectra were registered on Perkin-Elmer FT-600 spectrometer. ^{1}H, ^{13}C, ^{31}P spectra were recorded on a Bruker spectrometers at 400, 101, and 162 MHz, respectively, in δ ppm using TMS as internal standard. Elemental analyses (C, H, and N) were carried out with a Perkin-Elmer 2400 CHN elemental analyzer model 1106. Coupling constants J are in Hertz. Multiplicity is indicated by one of the following: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), ddd (doublet of doublet of doublet), m (multiplet), and chemical shifts are given in ppm and calibrated with DMSO-d_6. All reactions were monitored by thin-layer chromatography with silica gel Merck 60 F254 percolated aluminum plates (0.25 mm). The visualization was performed with a UV light at 254 nm and ninhydrin solution as developing agents.

Synthesis of 3-acetylcoumarin (1)

A mixture of salicylaldehyde (1 mmol) and ethyl acetoacetate (1.2 mmol) was cooled and maintained at 0–5 °C. Few drops of piperidine were added dropwise with continuous stirring. The reaction mixture was left overnight, resulting in the formation of a yellow-colored solid that was washed by ether and purification by recrystallization (EtOH/CHCl$_3$) 1:3 mixture gave 3-acetylcoumarin as fine yellow needles in good yields. Isolation and spectral data of this compound were reported in the literature [27, 52].

Synthesis of 3-(bromoacetyl)-coumarin (2) and 2-bromo-1-phenylethan-1-one (4)

3-(Bromoacetyl)-coumarin (II) and 2-bromo-1-phenylethan-1-one were prepared by the methods reported in the literature [53]. 3-Acetylcoumarin **1** (10 mmol) and acetophenone (10 mmol) were dissolved in alcohol-free chloroform (20 mL) and a solution of bromine (10 mmol) in chloroform (5 mL) was added dropwise from a dropping funnel. The mixture was stirred at room temperature for 15 min, then the mixture was heated for 20 min on a water-bath to expel most of the hydrogen bromide. The solid obtained was washed by ether and purification by recrystallization from glacial acetic acid gave 3-(bromoacetyl)-coumarin or 2-bromo-1-phenylethan-1-one as white shiny needles in good yields.

Synthesis of 3-(2-amino-1,3-thiazol-4-yl)coumarin (3) and 5-phenylthiazol-2-amine (5)

3-(2-Amino-1,3-thiazol-4-yl)coumarin and 5-phenylthiazol-2-amine were prepared by a mixture of Thiourea (5 mmol) and a solution of 3-(bromoacetyl)-coumarin (5 mmol) or 2-bromo-1-phenylethan-1-one in boiling ethanol (20 mL). The mixture was refluxed for 1 h, then cooled and neutralized with aqueous ammonia (NH$_4$Cl). The solid obtained was filtered off and washed with ethanol without recrystallization or other purification. The product was obtained in 90% yield [54].

3-(2-Amino-1,3-thiazol-4-yl)coumarin (3)

It was obtained as a yellow powder. Yield: 90%; m.p. 228–229 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.61 (ddd, J = 8.9, 7.3, 1.7 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.37 (td, J = 7.5, 1.1 Hz, 1H), 7.19 (s, 2H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.93, 159.21, 152.66, 138.60, 131.94, 131.47, 129.14, 125.14, 120.87, 119.75, 116.71, 116.28, 109.18.

General procedure for the synthesis of quinoline derivatives (6a–d)

To a solution of dimethylformamide (3 eq) in a flask equipped with a drying tube at 0 °C, phosphorus oxychloride (POCl$_3$) (7 eq) was added dropwise with stirring. Then, to this solution, add acetanilide derivatives (1 mmol). The reaction mixture was stirred and refluxed at 80–90 °C for a time ranging between 4 and 15 h. After the completion reaction, the mixture was cooled and poured in ice-cold water and stirred for 30 min, and then filtered and washed well with water and dried. The compounds were purified by recrystallization from either ethyl acetate.

2-Chloro-3-formyl-6-méthylquinoline (6b)

It was obtained as a yellow powder. Yield: 92%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.83 (s, 1H), 8.00 (t, J = 1.4 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.82 (dd, J = 8.6, 2.0 Hz, 1H), 2.55–2.49 (m, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 189.88, 148.54, 147.66, 141.03, 138.56, 136.44, 129.13, 127.96, 126.77, 21.51.

General procedure for the synthesis of quinolone derivatives (7a–d)

2-Chloro-3-formyl quinoline derivatives were treated with 70% acetic acid (CH$_3$CO$_2$H) aqueous solution (200 mL)

between 70 and 95 °C for 12 h. Then the solution was cooled to room temperature and filtered off without recrystallization. The products were obtained in excellent yield.

6-Methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (7c)

It was obtained as an orange powder; yield: 85%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 10.25 (d, $J = 0.8$ Hz, 1H), 8.42 (s, 1H), 7.44 (dd, $J = 2.2$, 1.1 Hz, 1H), 7.31 (d, $J = 2.3$ Hz, 2H), 3.80 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 190.31, 161.51, 154.97, 142.15, 136.49, 126.20, 124.07, 119.13, 117.25, 111.58, 56.01.

General procedure for the synthesis of quinoline derivatives (8a–b)

2-Hydroxy-1,2-dihydroquinoline-3-carbaldehyde derivatives were prepared by mixture of (5 mmol) of 2-chloroquinoline-3-carbaldehyde derivatives with 20 mL of clorohydric acid (HCl 37%) at reflux for 16 h. Excess water was added, and the reaction was stirred at room temperature for 45 min to have a yellow precipitate. The product is recovered directly after vacuum filtration and dried.

2-Hydroxy-6-methyl-1,2-dihydroquinoline-3-carbaldehyde (8b)

It was obtained as a yellow powder; yield: 85%; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 10.24 (s, 1H), 8.41 (d, $J = 0.6$ Hz, 1H), 7.71–7.66 (m, 1H), 7.49 (dd, $J = 8.5$, 2.0 Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 2.35 (s, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 190.28, 161.81, 142.52, 139.75, 135.59, 132.22, 130.49, 126.02, 118.55, 115.82, 20.74.

General procedure for the synthesis of α-aminophosphonates derivatives (9a–h) and (10i–l)

In a 10 mL round bottom flask taken a mixture of aldehyde derivatives (quinoline or quinolone) (1 mmol) with 1 mmol of 3-(2-amino-1,3-thiazol-4-yl)coumarin or 5-phenylthiazol-2-amine, and TEAA (1 mL) as a catalyst at room temperature. Then triethylphosphite (1 mmol) was added. The reaction mixture was exposed to US irradiation for the appropriate time. After completion of the reaction, as indicated by TLC, 5 mL of distilled water was added to the mixture. The ionic liquid was dissolved in water and filtered off. The separated product was washed with water. The solid product was purified by recrystallization in ethanol. Compounds (**9a–h**) and (**10i–l**) were obtained with 70–88% yield.

Diethyl((2-chloroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (9a)

It was obtained as a white powder; yield: 73%; m.p. 237–238 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.12 (dd, $J = 8.7$, 5.4 Hz, 1H), 8.59 (d, $J = 3.7$ Hz, 2H), 8.06–7.93 (m, 2H), 7.93–7.70 (m, 2H), 7.72–7.63 (m, 1H), 7.62 (td, $J = 7.7$, 1.6 Hz, 1H), 7.59 (s, 1H), 7.42 (dt, $J = 7.3$, 3.1 Hz, 2H), 6.14 (dd, $J = 22.0$, 8.6 Hz, 1H), 4.20 (dq, $J = 8.5$, 7.1 Hz, 2H), 4.09–3.95 (m, 1H), 3.98–3.82 (m, 1H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.07 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.36 (d, $J_{C-P} = 13.8$ Hz), 159.04, 152.70, 150.56 (d, $J_{C-P} = 6.8$ Hz), 146.69, 142.98, 138.77, 138.42 (d, $J_{C-P} = 4.9$ Hz), 132.10, 131.67, 130.32, 128.92, 128.34, 128.19 (d, $J_{C-P} = 12.1$ Hz), 127.20 (d, $J_{C-P} = 2.7$ Hz), 125.30, 120.82, 119.64, 116.38, 111.01, 63.77 (d, $J_{C-P} = 6.8$ Hz), 63.33 (d, $J_{C-P} = 7.0$ Hz), 53.09, 51.53, 46.11, 16.77 (d, $J_{C-P} = 5.3$ Hz), 16.50 (d, $J_{C-P} = 5.4$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 19.74; Anal. Calcd. for $C_{26}H_{23}ClN_3O_5PS$: C, 57.17; H, 4.17; N, 7.56. Found: C, 55.69; H, 4.38; N, 7.43.

Diethyl((2-chloro-8-methylquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (9b)

It was obtained as a green powder; yield: 70%; m.p. 130–132 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.10 (dd, $J = 8.7$, 5.3 Hz, 1H), 8.58 (s, 1H), 8.52 (d, $J = 2.9$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 7.75 (dd, $J = 8.0$, 1.6 Hz, 3H), 7.65–7.59 (m, 1H), 7.58 (s, 1H), 7.51 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.46–7.37 (m, 3H), 6.12 (dd, $J = 22.0$, 8.7 Hz, 1H), 4.19 (dq, $J = 8.6$, 7.0 Hz, 2H), 4.05–3.77 (m, 2H), 3.02 (q, $J = 7.3$ Hz, 1H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.06 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.36 (d, $J_{C-P} = 13.8$ Hz), 159.05, 152.70, 150.48 (d, $J_{C-P} = 6.9$ Hz), 147.00, 142.99, 141.97, 138.78, 138.13 (d, $J_{C-P} = 4.9$ Hz), 132.08, 130.31, 129.20, 128.91, 127.96, 127.03, 125.30, 120.83, 119.64, 116.37, 110.93, 79.76, 79.43, 79.10, 63.71 (d, $J_{C-P} = 7.0$ Hz), 63.30 (d, $J_{C-P} = 6.9$ Hz), 53.02, 51.46, 46.04, 21.85, 16.76 (d, $J_{C-P} = 5.4$ Hz), 16.48 (d, $J_{C-P} = 5.3$ Hz), 9.00; ^{31}P-NMR (162 MHz, DMSO-d_6) δ 19.91; Anal. Calcd. for $C_{27}H_{25}ClN_3O_5PS$: C, 56.89; H, 4.42; N, 7.37. Found: C, 56.37; H, 4.82; N, 7.54.

Diethyl((2-oxo-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (9c)

It was obtained as a white powder; yield: 86%; m.p. 204–205 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.64 (dd, $J = 9.2$, 3.9 Hz, 1H), 8.53 (s, 1H), 8.09 (d, $J = 3.5$ Hz, 1H), 7.80 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.67–7.59 (m, 2H), 7.58 (s, 1H), 7.50 (td, $J = 7.9$, 7.4, 1.3 Hz, 1H), 7.46–7.36 (m, 2H), 7.35–7.29 (m, 1H), 7.19 (ddd, $J = 8.1$,

7.2, 1.1 Hz, 1H), 6.01 (dd, $J = 20.9$, 9.2 Hz, 1H), 4.14 (dddd, $J = 10.6$, 8.1, 5.7, 3.4 Hz, 2H), 4.11–3.91 (m, 2H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.13 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.59 (d, $J_{C-P} = 10.8$ Hz), 161.27 (d, $J_{C-P} = 5.4$ Hz), 159.16, 152.71, 143.21, 138.69 (d, $J_{C-P} = 8.7$ Hz), 137.83 (d, $J_{C-P} = 6.3$ Hz), 132.03, 130.95, 129.70, 128.98, 128.24, 125.24, 122.58, 121.00, 119.72, 119.25 (d, $J_{C-P} = 3.0$ Hz), 116.40, 115.49, 110.34, 63.25 (d, $J_{C-P} = 6.8$ Hz), 63.04 (d, $J_{C-P} = 6.9$ Hz), 49.65, 16.73 (d, $J_{C-P} = 5.5$ Hz), 16.59 (d, $J_{C-P} = 5.6$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 21.40; Anal. Calcd. for $C_{26}H_{24}N_3O_6PS$: C, 58.10; H, 4.50; N, 7.82. Found: C, 58.66; H, 4.11; N, 7.44.

Diethyl((6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl) phosphonate (9d)

It was obtained as a yellow powder; yield: 84%; m.p. 275–276 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 8.65 (dd, $J = 9.2$, 3.8 Hz, 1H), 8.53 (s, 1H), 8.03 (d, $J = 3.5$ Hz, 1H), 7.79 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.62 (ddd, $J = 8.5$, 7.4, 1.6 Hz, 1H), 7.58 (s, 1H), 7.46–7.36 (m, 3H), 7.32 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 1H), 6.01 (dd, $J = 20.9$, 9.2 Hz, 1H), 4.21–3.90 (m, 4H), 2.34 (s, 3H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.13 (t, $J = 7.1$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.60 (d, $J_{C-P} = 11.0$ Hz), 161.19 (d, $J_{C-P} = 5.3$ Hz), 159.16, 152.70, 143.21, 138.72, 137.61 (d, $J_{C-P} = 6.0$ Hz), 136.65, 132.10 (d, $J_{C-P} = 17.8$ Hz), 131.61, 129.59, 128.97, 127.67, 125.23, 121.00, 119.71, 119.21 (d, $J_{C-P} = 2.9$ Hz), 116.39, 115.41, 110.31, 63.22 (d, $J_{C-P} = 6.7$ Hz), 63.03 (d, $J_{C-P} = 6.9$ Hz), 49.66, 48.11, 20.79, 16.74 (d, $J_{C-P} = 5.5$ Hz), 16.59 (d, $J_{C-P} = 5.5$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 22.12; Anal. Calcd. for $C_{27}H_{26}N_3O_6PS$: C, 58.80; H, 4.75; N, 7.62. Found: C, 58.30; H, 4.80; N, 7.88.

Diethyl((6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl) phosphonate (9e)

It was obtained as an orange powder; yield: 83%; m.p. 242–244 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.63 (dd, $J = 9.1$, 4.1 Hz, 1H), 8.52 (d, $J = 6.4$ Hz, 2H), 8.05 (d, $J = 3.5$ Hz, 1H), 7.81 (ddd, $J = 15.0$, 7.8, 1.6 Hz, 2H), 7.66–7.55 (m, 3H), 7.52 (s, 1H), 7.40 (dt, $J = 19.7$, 7.7 Hz, 4H), 7.30–7.23 (m, 1H), 7.19–7.11 (m, 4H), 6.01 (dd, $J = 21.0$, 9.0 Hz, 1H), 4.22–4.13 (m, 1H), 4.17–4.06 (m, 1H), 4.10–3.91 (m, 2H), 3.79 (s, 3H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.14 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.89, 166.52 (d, $J_{C-P} = 11.1$ Hz), 160.85 (d, $J_{C-P} = 5.2$ Hz), 159.18 (d, $J_{C-P} = 8.8$ Hz), 154.78, 152.66 (d, $J_{C-P} = 4.6$ Hz), 143.77, 143.19,

138.64 (d, $J_{C-P} = 18.2$ Hz), 137.39 (d, $J_{C-P} = 6.2$ Hz), 133.14, 131.95 (d, $J_{C-P} = 10.4$ Hz), 130.06, 129.03 (d, $J_{C-P} = 18.7$ Hz), 125.12, 120.97 (d, $J_{C-P} = 3.0$ Hz), 120.22, 119.73 (d, $J_{C-P} = 5.8$ Hz), 116.81, 116.32 (d, $J_{C-P} = 11.5$ Hz), 110.31, 109.50, 109.19, 63.23 (d, $J_{C-P} = 6.6$ Hz), 63.05 (d, $J_{C-P} = 6.9$ Hz), 55.96, 49.74, 48.19, 16.74 (d, $J_{C-P} = 5.6$ Hz), 16.60 (d, $J_{C-P} = 5.6$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 21.12; Anal. Calcd. for $C_{27}H_{26}N_3O_7PS$: C, 57.14; H, 4.62; N, 7.40. Found: C, 56.96; H, 4.70; N, 7.20.

Diethyl((8-methyl-2-oxo-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl) phosphonate (9f)

It was obtained as a green powder; yield: 85%; m.p. 152–154 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.61 (dd, $J = 9.3$, 3.8 Hz, 1H), 8.52 (d, $J = 7.9$ Hz, 2H), 8.05 (d, $J = 3.5$ Hz, 1H), 7.81 (ddd, $J = 10.9$, 7.8, 1.6 Hz, 2H), 7.61 (dddd, $J = 8.7$, 7.1, 5.3, 1.6 Hz, 2H), 7.57 (s, 1H), 7.52 (d, $J = 7.2$ Hz, 2H), 7.47–7.32 (m, 3H), 7.13 (d, $J = 13.5$ Hz, 2H), 7.02 (dd, $J = 8.1$, 1.5 Hz, 1H), 5.99 (dd, $J = 20.8$, 9.3 Hz, 1H), 4.22–3.89 (m, 4H), 2.37 (s, 3H), 1.17 (dt, $J = 38.5$, 7.0 Hz, 6H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.89, 166.64, 161.41 (d, $J_{C-P} = 5.5$ Hz), 159.19 (d, $J_{C-P} = 8.4$ Hz), 152.67 (d, $J_{C-P} = 4.7$ Hz), 143.76, 143.21, 141.14, 138.75 (d, $J_{C-P} = 8.0$ Hz), 138.56, 131.96 (d, $J_{C-P} = 10.2$ Hz), 129.05 (d, $J_{C-P} = 16.0$ Hz), 128.38, 128.08, 125.18 (d, $J_{C-P} = 9.7$ Hz), 124.01, 120.97 (d, $J_{C-P} = 3.3$ Hz), 119.74 (d, $J_{C-P} = 6.0$ Hz), 117.16, 116.33 (d, $J_{C-P} = 11.0$ Hz), 115.21, 110.28, 109.19, 63.19 (d, $J_{C-P} = 6.9$ Hz), 63.01 (d, $J_{C-P} = 6.8$ Hz), 21.86, 16.73 (d, $J_{C-P} = 5.5$ Hz), 16.58 (d, $J_{C-P} = 5.7$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 21.22; Anal. Calcd. for $C_{27}H_{26}N_3O_6PS$: C, 58.80; H, 4.75; N, 7.62. Found: C, 58.22; H, 4.17; N, 7.86.

Diethyl((2-hydroxy-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (9g)

It was obtained as a white powder; yield: 78%; m.p. 173–177 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 8.65 (dd, $J = 9.2$, 3.9 Hz, 1H), 8.53 (s, 1H), 8.10 (d, $J = 3.5$ Hz, 1H), 7.80 (dd, $J = 7.7$, 1.5 Hz, 1H), 7.63 (ddd, $J = 13.5$, 7.3, 2.8 Hz, 2H), 7.58 (s, 1H), 7.54–7.23 (m, 5H), 7.19 (t, $J = 7.5$ Hz, 1H), 6.02 (dd, $J = 20.9$, 9.2 Hz, 1H), 4.22–3.92 (m, 4H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.14 (t, $J = 7.0$ Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.59 (d, $J_{C-P} = 11.0$ Hz), 161.28 (d, $J_{C-P} = 5.2$ Hz), 159.15, 152.70, 143.21, 138.69 (d, $J_{C-P} = 7.6$ Hz), 137.83 (d, $J_{C-P} = 6.0$ Hz), 132.02, 130.95, 129.71, 128.98, 128.24, 125.23, 122.57, 121.00, 119.71, 119.24, 116.39, 115.50, 110.34, 63.26 (d, $J_{C-P} = 6.7$ Hz), 63.04 (d, $J_{C-P} = 6.8$ Hz), 49.66, 48.11, 16.73 (d, $J_{C-P} = 5.5$ Hz), 16.59 (d, $J_{C-P} = 5.6$ Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 19.74; Anal. Calcd. for

$C_{26}H_{26}N_3O_6PS$: C, 57.88; H, 4.86; N, 7.79. Found: C, 57.72; H, 4.56; N, 7.68.

Diethyl((2-hydroxy-6-methyl-1,2-dihydroquinolin-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl) phosphonate (9h)

It was obtained as a white powder; yield: 71%; m.p. 209–210 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.94 (d, J = 3.9 Hz, 1H), 7.52–7.47 (m, 1H), 7.36–7.29 (m, 1H), 7.22 (d, J = 8.3 Hz, 1H), 6.15 (dd, J = 13.9, 6.2 Hz, 1H), 5.32–5.22 (m, 1H), 4.13–3.89 (m, 4H), 2.35 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 161.05 (d, J_{C-P} = 5.6 Hz), 137.77 (d, J_{C-P} = 6.5 Hz), 136.47 (d, J_{C-P} = 1.8 Hz), 132.02, 131.46, 131.07, 127.85, 119.41 (d, J_{C-P} = 3.3 Hz), 115.31, 62.74 (d, J_{C-P} = 6.7 Hz), 62.57 (d, J_{C-P} = 6.8 Hz), 20.84, 16.83, 16.77, 16.71; ^{31}P-NMR (162 MHz, DMSO-d_6) δ 19.90; Anal. Calcd. for $C_{27}H_{28}N_3O_6PS$: C, 58.58; H, 5.10; N, 7.59. Found: C, 58.87; H, 4.79; N, 7.12.

Diethyl ((2-chloroquinolin-3-yl)((5-phenylthiazol-2-yl) amino)methyl)phosphonate (10 i)

It was obtained as a yellow powder; yield: 88%; m.p. 201–203 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.49 (dd, J = 9.7, 3.5 Hz, 1H), 8.08 (d, J = 3.6 Hz, 1H), 7.87–7.75 (m, 2H), 7.62 (dd, J = 7.9, 1.3 Hz, 1H), 7.54–7.45 (m, 1H), 7.40–7.29 (m, 3H), 7.33–7.12 (m, 3H), 7.11 (s, 1H), 6.05 (dd, J = 21.1, 9.6 Hz, 1H), 4.21–3.86 (m, 4H), 1.20 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 168.62, 167.27 (d, J_{C-P} = 10.0 Hz), 161.15 (d, J_{C-P} = 5.1 Hz), 149.72, 138.61, 137.69 (d, J_{C-P} = 6.2 Hz), 135.09, 130.90, 129.82, 128.89, 128.18, 127.79, 126.00 (d, J_{C-P} = 2.7 Hz), 122.54, 119.23 (d, J_{C-P} = 3.0 Hz), 115.48, 103.02, 101.93, 63.20 (d, J_{C-P} = 6.7 Hz), 62.95 (d, J_{C-P} = 7.1 Hz), 49.44, 47.89, 16.70 (d, J_{C-P} = 5.5 Hz), 16.57 (d, J_{C-P} = 5.5 Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 21.14; Anal. Calcd. for $C_{23}H_{23}ClN_3O_3PS$: C, 56.62; H, 4.75; N, 8.61. Found: C, 56.11; H, 4.23; N, 8.92.

Diethyl((2-chloro-8-methylquinolin-3-yl)((5-phenylthiazol-2-yl)amino)methyl)phosphonate (10j)

It was obtained as a yellow powder; yield: 84%; m.p. 131–132 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 3.2 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.51 (dd, J = 8.4, 1.7 Hz, 1H), 6.64 (dd, J = 16.3, 5.7 Hz, 1H), 5.37 (dd, J = 13.6, 5.7 Hz, 1H), 4.14–3.87 (m, 4H), 2.53 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 149.01 (d, J_{C-P} = 7.0 Hz), 147.11 (d, J_{C-P} = 2.4 Hz), 141.79, 138.89 (d, J_{C-P} = 5.1 Hz), 130.57, 130.12, 128.27, 126.94,

125.40 (d, J_{C-P} = 2.8 Hz), 67.19, 65.53, 63.12 (d, J_{C-P} = 7.0 Hz), 62.81 (d, J_{C-P} = 6.9 Hz), 21.89, 16.79 (d, J_{C-P} = 5.4 Hz), 16.68 (d, J_{C-P} = 5.3 Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 20.65; Anal. Calcd. for $C_{24}H_{25}ClN_3O_3PS$: C, 57.43; H, 5.02; N, 8.37. Found: C, 56.89; H, 5.34; N, 8.76.

Diethyl((6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)((5-phenylthiazol-2-yl)amino)methyl)phosphonate (10k)

It was obtained as a white powder; yield: 90%; m.p. 272–274 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.64 (dd, J = 9.3, 3.8 Hz, 1H), 8.53 (s, 1H), 8.03 (d, J = 3.5 Hz, 1H), 7.85–7.73 (m, 1H), 7.68–7.58 (m, 1H), 7.57 (s, 1H), 7.54–.44 (m, 1H), 7.46–7.35 (m, 3H), 7.27 (ddd, J = 41.4, 8.4, 2.1 Hz, 3H), 6.01 (dd, J = 20.9, 9.3 Hz, 1H), 4.23–3.90 (m, 4H), 2.34 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.19–1.08 (m, 3H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 166.60 (d, J_{C-P} = 10.8 Hz), 161.16, 159.16, 152.70, 143.21, 138.73, 136.64, 132.21, 132.02, 131.63, 129.58, 128.97, 127.85, 127.67, 125.24, 120.99, 119.71, 119.23, 116.39, 116.28, 115.41, 115.31, 110.31, 63.23 (d, J_{C-P} = 6.9 Hz), 63.04 (d, J_{C-P} = 6.9 Hz), 62.78, 62.32, 49.66, 48.11, 46.26, 31.14, 20.84, 20.79, 16.74 (d, J_{C-P} = 5.6 Hz), 16.59 (d, J_{C-P} = 5.5 Hz), 9.10: ^{31}P-NMR (162 MHz, DMSO-d_6) δ 19.79; Anal. Calcd. for $C_{24}H_{26}N_3O_4PS$: C, 59.62; H, 5.42; N, 8.69. Found: C, 59.12; H, 5.31; N, 8.17.

Diethyl((6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)((5-phenylthiazol-2-yl)amino)methyl)phosphonate (10l)

It was obtained as an orange powder; yield: 89%; m.p. 138–139 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.48 (dd, J = 9.5, 3.7 Hz, 1H), 8.09–7.92 (m, 2H), 7.94–7.76 (m, 3H), 7.67 (tdd, J = 9.9, 6.2, 4.2 Hz, 1H), 7.48–7.18 (m, 7H), 7.22–7.13 (m, 1H), 7.17–7.05 (m, 3H), 7.01 (d, J = 13.3 Hz, 1H), 6.06 (dd, J = 21.2, 9.4 Hz, 1H), 5.30 (dd, J = 13.4, 5.8 Hz, 1H), 4.22–4.11 (m, 1H), 4.15–4.00 (m, 2H), 3.99–3.89 (m, 1H), 3.80 (s, 3H), 1.16 (dt, J = 32.3, 7.0 Hz, 6H); ^{13}C-NMR (101 MHz, DMSO-d_6) δ 168.66, 167.27 (d, J_{C-P} = 10.3 Hz), 160.76 (d, J_{C-P} = 5.3 Hz), 154.79, 149.73, 137.30 (d, J_{C-P} = 6.1 Hz), 135.11, 133.13, 130.19, 128.90, 128.62, 127.79, 127.62, 126.01 (d, J_{C-P} = 2.8 Hz), 120.20, 120.05, 119.79, 116.83, 116.68, 109.81, 109.47, 103.01, 101.95, 63.20 (d, J_{C-P} = 6.6 Hz), 62.98 (d, J_{C-P} = 6.9 Hz), 55.96, 49.57, 48.02, 16.70 (d, J_{C-P} = 5.5 Hz), 16.58 (d, J_{C-P} = 5.5 Hz); ^{31}P-NMR (162 MHz, DMSO-d_6) δ 21.31; Anal. Calcd. for $C_{24}H_{26}N_3O_5PS$: C, 57.71; H, 5.25; N, 8.41. Found: C, 57.11; H, 4.89; N, 7.98.

Pharmacological/biological assays

The in vitro antimicrobial activity of all synthesized compounds was screened in terms of MIC values against six

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Gram-positive bacteria: *Bacillus cereus, Staphylococcus aureus* resistant to ciprofloxacin, *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 6538, *Enterococcus faecalis* ATCC 29212, *Enterococcus faecalis* vancomycin-resistant, and 16 Gram-negative bacteria: *Escherichia coli* ATCC 25922, *Escherichia coli* ESBL (enlarged specter β-lactamase) producer, *Escherichia coli* ESBL producer, *Escherichia coli* resistant to ciprofloxacin, *Klebsiella pneumoniae* Carbapenem-resistant (KpC+), *Klebsiella pneumoniae* Carbapenem-sensitive (KpC–), *Serratia marcescens, Salmonella typhi* 14028, *Pseudomonas aeruginosa* ATCC 9027, *Pseudomonas aeruginosa* imipenem-resistant (VIM-2), *Acinetobacter baumannii* (NDM-1), *Acinetobacter baumannii.* OXA-23, *Enterobacter cloacae* fosfomycin resistant, *Citrobacter sp, E.coli mcr-1, E.coli* ATCC 8739, and fungal strains *Candida albicans* and *Saccharomyces ceriviceae.* All of them were isolated from patients hospitalized in the various departments at Annaba Hospital, Algeria. Their identification and susceptibility profile are reported by Toumi et al. [55] and Meliani et al. [56]. Four standard drugs Imipenem, Ciprofloxacin, Amikacine, and fluconazole were used as positive controls, while DMSO was used as a negative control in this study. The MIC of the compounds was determined by broth micro-dilution method and DMSO was used in µg/mL [57]. The microbial suspensions were prepared in Muller–Hinton broth from test organisms sub-cultured on nutrient agar and incubated at 37 °C for 24 h.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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