Molecular Diversity
https://doi.org/10.1007/s11030-021-10242-2

ORIGINAL ARTICLE

Synthesis and potent antimicrobial activity of novel coumarylthiazole α-aminophosphonates derivatives

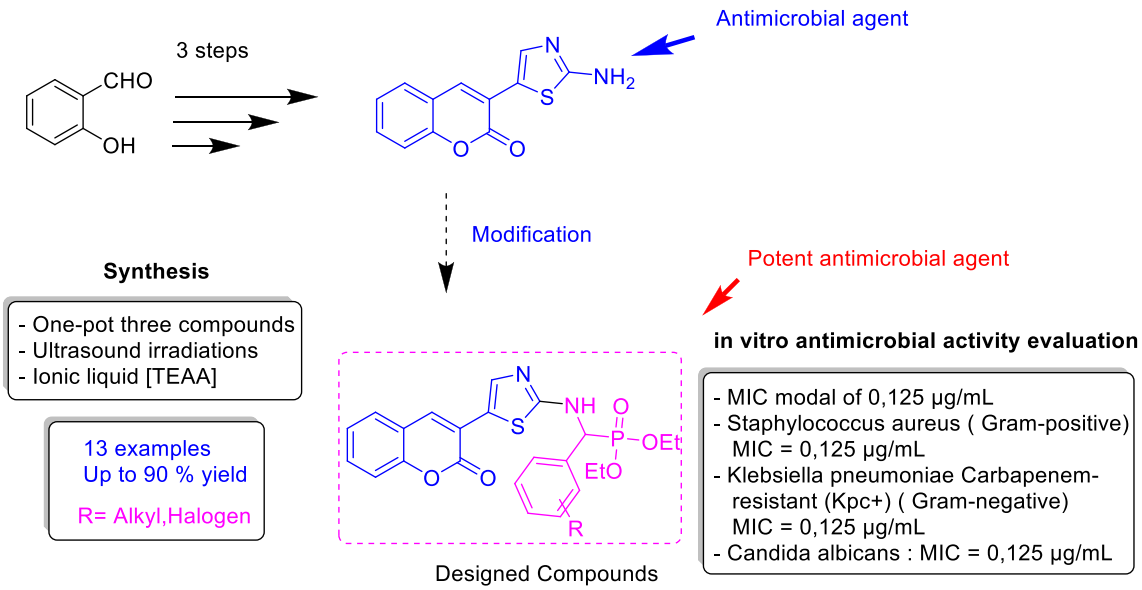
Bilal Litim[1] · Zinelaabidine Cheraiet[2] · Saida Meliani[3] · Abdelghani Djahoudi[4] · Abbes Boukhari[1]

Received: 24 March 2021 / Accepted: 28 May 2021

Abstract

Herein, we reported a novel series of *α*-aminophosphonates derivatives (IV)a–m bearing an important pharmacophore coumarylthiazole moiety. All the new compounds have been synthesized via Kabachnik–Fields reaction under ultrasonic irradiation. The products were obtained in good yield with a simple workup and were confirmed using various spectroscopic methods. All these compounds (IV)a–m were screened for their in vitro for antimicrobial activity against thirteen Gram-negative bacteria and five Gram-positive bacteria and Candida albicans strains. The results showed that all the synthesized compounds exhibited moderate antibacterial activities against both references and multidrug-resistant and antifungal strains. The compound **(IV)e** showed the highest activities against all pathogens of the tested microbial strains with MIC of 0.125 µg/mL. The compounds **(IV)h**, **(IV)f**, **(IV)b**, and **(IV)d** exhibited moderate and promising activities with MIC of 0.125 µg/mL. Structure–activity relationship revealed that inhibitory activity of the synthesized compounds is related to the type of the substituted group on phenyl rings, and these results showed that the electron-donating groups at *ortho* and *para* positions have a high relationship increasing antimicrobial activities than the electron-withdrawing groups. These results confirm that coumarylthiazole α-aminophosphonates compounds can be potential antimicrobial drugs candidate.

Graphic abstract



Keywords Coumarylthiazole · α-aminophosphonates · Antimicrobial · Multidrug-resistant · Kabachnik–Fields reaction

✉ Bilal Litim
billellitim23@gmail.com

Extended author information available on the last page of the article

Published online: 12 June 2021

Introduction

According to a report by World Health Organization (WHO), multidrug-resistant pathogen strains are among the biggest challenges in treating bacterial infections diseases worldwide, urgent strategy is required to fight antimicrobial resistance expected to cause more financial crisis by forcing 24 million people into extreme poverty by 2030 and causing 10 million deaths annually by 2050 [1]. Based on these facts and due to the high degree of antimicrobial resistance, the discovery of new and effective antibacterial drugs must be discovered to overcome bacterial resistance and develop effective treatments [2].

Current strategies in the pharmacological research of new lead compounds mostly refer to a large collection of molecules proven to be broadly and useful as therapeutic agents such as pyrazolone and its derivatives [3, 4], benzoxazole [5], indole [6], pyrimidine analogs [7]. Therefore, compounds that contain thiazole heterocycles are well known in a variety of natural products [8], thiazole derivatives exhibit a broad spectrum in various synthetic pharmaceuticals and medicinal chemistry [9] such as antimicrobial and antimalarial agents [10], Alzheimer [11], antiproliferative agents [12], anti-cancer agents [13], and anti-inflammatory [14]. In addition, Coumarin and its derivatives constitute an important class of heterocyclic compounds that hold an imperative place in medicinal chemistry. They are distributed in nature and possess a large array of pharmacological activities like antibacterial, anticoagulant, anti-HIV, antioxidant, antitubercular, antihypertensive, anticonvulsant, antifungal, antihyperglycemic, inhibition of diverse enzymes, and anticancer [15, 16]. Moreover, the biological activities of the different analogs of the synthesized coumarins are influenced by their substitution in different positions, among these derivatives the coumarins having various substituted thiazole rings show promising biological activities [17]. Recently, many scientific studies on analogs of the coumarylthiazole motif having potential biological activities such as anti-acetylcholinesterase [18] **1**, anti-inflammatory [19], antibacterial and anti-tuberculosis agents [20] **2**, as well as inhibition of carbonic anhydrase and antioxidant have been carried out [21, 22] **3.4** (Fig. 1).

Recently, the synthesis of α-aminophosphonates has attracted the attention of many scientific researchers in organic and medicinal chemistry [23], due to structural analogies to amino acids and their various pharmacological properties [24], such as anti-Alzheimer [25], antimicrobial [26], antiviral [27], and antioxidant [28]. Access to α-aminophosphonates moiety has been achieved by various methods [29]. The Kabachnik–Fields reaction is one and the simplest of the most practical approaches for α-aminophosphonate syntheses described in the literature. The reaction generally requires various catalysts, such as ethyl lactate [30], phenyl phosphonic acid [31], xanthan sulfuric acid [32], $SnCl_2$ [33], TiO_2 [34], $FeCl_3$ [35], Amberlite-IR 120 [36], $Yb(PFO)_3$ [37], $SbCl_3/Al_2O_3$ [38], and CF_3CO_2H [39]. However, many of these catalysts suffer from at least one of the following drawbacks such as low yields, long reaction times, high reaction temperature, tedious workup, use unrecyclable catalysts, so an inexpensive

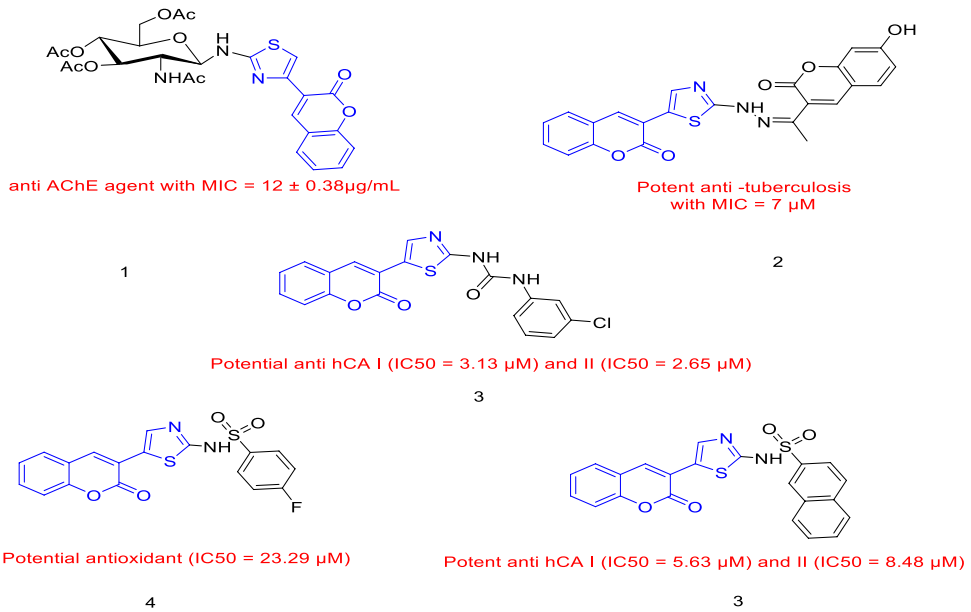


Fig. 1 Biological profile of coumarylthiazole derivatives

Scheme 1 Synthesis of new α-aminophosphonates substituted coumarylthiazole (IV)a–m derivatives

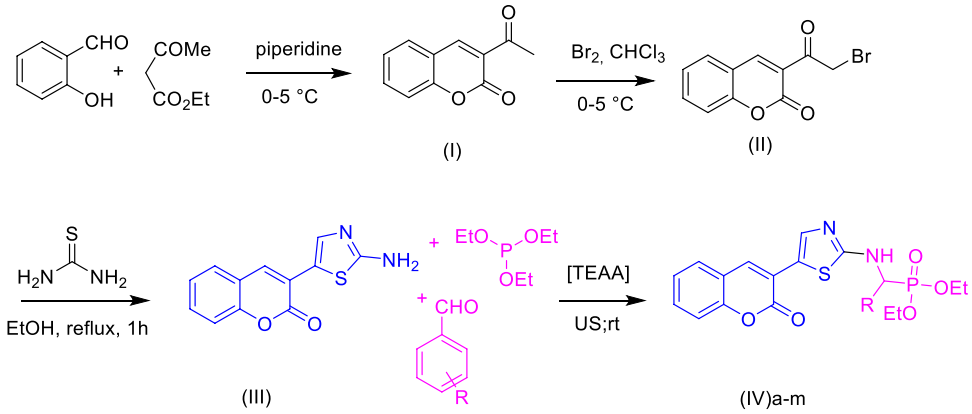


Table 1 Optimization of reaction conditions

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)[a]
1	CH_3CN	110	120	nr
2	$PhCH_3$	120	120	nr
3	THF	90	120	10
4	EtOH	80	120	30
5	EtOH/TEAA	80	120	52
6	TEAA/US	rt	10	92
7	TEAB/US	rt	60	20

Conditions: 1 mL TEAA (triethylammonium acetate), 1 mmol substrate, US (ultrasounds) 40 kHz

nr no reaction

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

alternative to α-aminophosphonates can be used, namely solvent-free and using green catalyst conditions is our aim [40].

In this work, we have synthesized and characterized novel α-aminophosphonates derivatives substituted with coumarylthiazole rings using Kabachnik–Fields reaction under ultrasonic irradiation and solvent-free conditions, the antimicrobial activities of the synthesized compound were evaluated against references and multidrug-resistant bacteria and Candida albicans strain.

Results and discussion

Chemistry

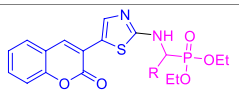
Coumarylthiazole derivatives are known for their potential antibacterial activity [20]. Our design strategy was based on the synthesis of new α-aminophosphonates containing coumarylthiazole scaffold. On the other hand, we thought that the presence of α-aminophosphonates moiety contributes to improving the biological activity against references and multidrug-resistant bacteria.

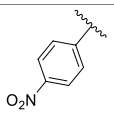
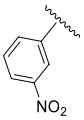
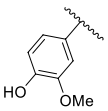
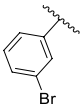
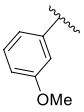
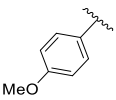
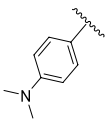
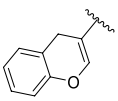
A new series of α-aminophosphonates derivatives (IV) a–m containing an important pharmacophore (coumarylthiazole heterocycle) were synthesized, and using Kabachnik–Fields reaction conditions, the reaction to give the target compounds (IV)a–m it was started from 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (III), aldehyde, and triethyl phosphite under ultrasound irradiation using a green ionic liquid [TEAA] as a catalyst at ambient temperature (Scheme 1). The reaction conditions, yields, and reaction times are summarized in Table 1.

The first step of the synthesis involved the formation of 3-acetylcoumarin (I) obtained by the condensation between salicylaldehyde and ethyl acetoacetate in ethanol at 0–5 °C in the presence of a catalytic amount of piperidine. The second precursor, 3-(2-bromoacetyl)-2H-chromen-2-one (II), was synthesized by brominating 3-acetyl coumarin in chloroform. 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (III) was obtained by reaction of compound (II) with thiourea in ethanol and neutralized with ammonia. Finally, compounds (IV) a-m were obtained when reacted 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (III), aldehyde, and triethyl phosphite via Kabachnik–Fields reaction under ultrasonic irradiation in the presence of ionic liquid [TEAA] as a catalyst. This procedure offers several advantages such as giving pure product without chromatography purification and high yield in a short time reaction (Scheme 1).

Firstly, we have reported Kabachnik–Fields reaction between 3-(2-aminothiazol-5-yl)-2H-chromen-2-one (III), benzaldehydes, and triethyl phosphite in different solvents such as toluene, THF, acetonitrile, and ethanol. After the reaction mixture was stirred at reflux for 120 min, no desired product was detected (Table 1, entries 1, 2, 3, and 4). The solvent has been found to have a remarkable effect on the evaluation of the reaction and the yields found vary around 0–30%. Then, we have wanted to improve these results by using an ionic liquid with an acid–base character of Brönsted [TEAA] as a solvent and catalyst. The reaction is carried out under reflux in ethanol and without solvent under ultrasonic irradiations. It was found that the reaction without solvent

Table 2 Ultrasound irradiations assisted synthesis of α-aminophosphonates in ionic liquid TEAA



Compound	R	Time (min)	Yield (%)	M.p. (°C)
a		30	83	204.0–205.7
b		20	75	221.3–222.4
c		15	82	243.4–244.2
d		10	87	184.0–188.0
e		30	65	262.1–263.4
f		150	73	212.6–213.1
g		30	90	215.4–216.6
h		30	75	193.5–194.4
i		60	69	228.9–229.7
j		120	76	236.8–237.5
k		180	65	207.1–208.3
l		25	92	210.5–211.4
m		30	91	213.1–214.2

Conditions: aldehyde (1 mmol), amine (1 mmol), triethylphosphite (1 mmol), TEAA (1 mL), 40 kHz

in ionic liquid [TEEA] and under ultrasonic irradiation was given the best yield (92%) after 10 min (Table 1, entries 5 and 6).

To present the effectiveness of TEAA as a catalyst in the synthesis of α-aminophosphonates, we have used another ionic liquid TEAB which has the same character as TEAA, the results showed that TEAA is more efficient than another ionic liquid (Table 1, entry 7).

All the new compounds (IV)a–m were characterized by spectroscopic techniques IR, ^{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. This confirmed the exact structure of the compounds (Table 2).

The infrared spectroscopic indicated the absorptions at 3418 cm^{-1} and 1233 cm^{-1} corresponded to (N–H) and (P=O) stretching, respectively, of α-aminophosphonates groups. Absorptions at 1540 cm^{-1} corresponded to imine group (C=N) stretching for thiazole ring, and absorptions at 1716 cm^{-1} corresponded to lactone group (O–C=O) stretching from coumarin rings. From the ^{1}H-NMR spectroscopic, it was possible to observe the presence of signals at $\delta = 1.2$ ppm and $\delta = 4.1$ ppm corresponded to methyl (**CH_3**–CH_2–O–P) and methylene (CH_3–**CH_2**–O–P), respectively, of phosphonates groups; the proton (N–H) of α-aminophosphonates groups was detected at $\delta = 8.9$ ppm, the signal between $\delta = 5.6$—6.5 ppm corresponded the proton from asymmetric Carbone (*C), the signals of protons corresponded the thiazole and coumarin rings were detected at $\delta = 7.5$ ppm and $\delta = 8.4$ ppm, respectively, and the signals corresponded to aromatic hydrogens were observed between $\delta = 7.46$—8.96 ppm. The ^{13}C-NMR spectroscopic analysis also confirmed the structural identity by observing the new characteristic type of doublets signals at $\delta = 16$ ppm and $\delta = 63$ ppm corresponded for methylene (**CH3–CH2–O–P**) and ethylene (CH3–CH2–O–P), respectively, due to the coupling of the carbon atoms with the phosphorus atoms (**J_{C-P}**), and the signals at $\delta = 16$ ppm and $\delta = 63$ ppm corresponded to methyl and methylene, respectively, of α-aminophosphonates groups, the signal corresponded the asymmetric Carbone (*C) was observed at $\delta = 53, 7$ ppm, the signals at $\delta = 159$ ppm and $\delta = 166, 63$ ppm relating to coumarin carbonyl and thiazole ring, respectively. The ^{31}P-NMR spectroscopic analysis was found to give a signal ranging between $\delta = 19.7$—20.2 ppm confirming the presence of the atom of phosphors for the phosphonates groups.

The structure attribution of proton–carbon of the representative compounds was further confirmed by 2D NMR (HSQC, HMBC) experiments (400 MHz). The HSQC spectra confirm all the vicinal correlation proton–carbon (1–2). And the HMBC spectra indicate and confirm the correlation between proton–carbon (1–3 and 1–4). The elemental analysis furthermore confirmed the assigned structures of all synthesized compounds.

Biological results

Recently, it is known that many synthetic coumarylthiazole derivatives have various pharmacological properties. Among these properties, they have interesting antimicrobial activity [41]. The literature reports reveal that the α-aminophosphonates derivatives displayed good antibacterial activity against both Gram-negative and Gram-positive bacterial strains [42].

We have considered that the synthesized compounds might possess certain antimicrobial activities due to a combination of coumarylthiazole and α-aminophosphonates moiety in the same scaffold.

All the newly synthesized compounds (IV)a–m have been evaluated in vitro for their antibacterial activity against the selected strains of Gram-negative and Gram-positive bacteria and one fungal strain, using the broth micro-dilution method. Dimethyl sulfoxide (DMSO) was used as a negative control. For the control test, we have used Imipenem, Ciprofloxacin, Amikacinekacine as a positive control to compare the minimal inhibitory concentration (MIC), the MIC values are reported in Tables 3 and 4.

The results clearly showed that all the tested compounds had excellent antimicrobial effects against the different bacteria strains ranging between 0.125—128 µg/mL compared with standard drugs (positive control). The highest activity was observed with the compound **(IV)e** with MIC values of 0.125 µg/mL against both Gram-negative and Gram-positive bacteria strains. In addition, four compounds **(IV)h**, **(IV)f**, **(IV)b**, and **(IV)d** also showed excellent activity with MIC values ranging between 0.125—64 µg/ML and 0.125—4 µg/mL against both Gram-negative and Gram-positive bacteria strain, respectively.

The compound (IV)e exhibited the strongest inhibition against *Escherichia coli ATCC 25922, Escherichia coli ESBL, (Kpc +),(Kpc_), Klebsiella pneumonia Sey Marseille, Serratia marcescens, Salmonella sp, Pseudomonas aeruginosa ATCC 27853, Pseudomonas aeruginosa imipenem-resistant (VIM-2.1), and Acinetobacter baumanni. OXA-23* with MIC values 0.125 µg/mL for Gram-negative bacteria strain, and high inhibition against *Bacillus cereus, Staphylococcus aureus ATCC25900, Staphylococcus aureus ATCC25923, and Staphylococcus aureus ATCC 29213* with MIC values 0.125 µg/mL for Gram-positive bacteria strain

Table 3 Values of MIC (µg/mL) of the synthesized α-aminophosphonates derivatives against the tested Gram-positive bacteria

	Bacillus cereus	Staph.aureus ATCC25900	Staph.aureus ATCC25923	Staph.aureus ATCC 29213	Enterococcus faecalis VANCO R	Condida albicans
(IV)a	4	++	++	0.125	4	++
(IV)b	0.5	4	0.125	0.125	++	++
(IV)c	4	0.5/4	1	1	16	1
(IV)d	4	0.125	0.125	0.125	++	4
(IV)e	0.125	0.125	0.125	0.125	++	0.125
(IV)f	2	++	0.125	0.125	0.125	2
(IV)g	32	++	++	0.5	0.125	1
(IV)h	0.5/64	++	++	0.25	0.125	1/64
(IV)i	0.125	8	0.125	++	0.125	0.125
(IV)j	0.125	2/128	0.125	++	0.125	0.125/16
(IV)k	0.125	4	0.5	128	0.25	0.5
(IV)l	0.125	++	16	++	0.125	0.125
(IV)m	2/128	++	0.5	8	1	128
Imipenem[a]	–	–	–	–	–	–
Ciprofloxacin[a]	–	–	–	–	–	–
Amikacine[a]	–	–	–	–	–	–
Fluconazole[a]	–	–	–	–	–	2

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

R resistant, *MIC* minimum inhibitory concentration

[a]Positive reference

was comparable and even more efficient than the standard drugs, Imipenem, Ciprofloxacin, and Amikacine. Furthermore, the following compounds (IV)h, (IV)f, (IV)b, and (IV)d have exceptional and strong inhibition activity against *Escherichia coli ATCC 25922, Escherichia coli ESBL, Salmonella, Pseudomonas aeruginosa ATCC 27853, and Pseudomonas aeruginosa imipenem-resistant (VIM-2.1)* with MIC values 0.125 µg/mL Gram-negative bacteria strain and against *Staphylococcus aureus ATCC25923, Staphylococcus aureus ATCC 29213* with MIC values 0.125 µg/mL Gram-positive bacteria strain. So all of these compounds can be considered as broad-spectrum potential antibacterial agents.

On the other hand, we were observed that the following multidrug-resistant bacteria strain *Pseudomonas aeruginosa imipenem-resistant (VIM-2.2), Acinetobacter baumanni (NDM-1), and Acinetobacter baumanni OXA-23* were exhibited less resistance against the synthesized compounds with MIC ranging between 0.125 and 128 µg/mL. These results can confirm effectively the potential inhibition of the synthesized compounds against multidrug resistance strains.

The in vitro antifungal activity of all the synthesized compounds (IV)a–m was screened against Candida albicans strain using the drug Fluconazole as a reference standard, four compounds (IV)e, (IV)i, (IV)j, and (IV)l were found having good and moderate promising activity with MIC values 0.125 µg/mL, the antifungal activity of the other compounds was found in the range of 1-128 µg/mL less than the drug fluconazole 2 µg/mL, and most of these compounds can be therefore considered as potential antifungal agents.

Based on the results of Tables 3 and 4, we were found that the synthesized compounds substituted with heterocyclic rings (IV)l and (IV)m have excellent and remarkable activity, the compound (IV)l exhibited a high inhibition against Bacillus cereus, Enterococcus faecalis resistant for vancomycin, and Candida albicans with MIC value 0.125 µg/mL. On the other hand, the compound (IV)m showed moderate and high inhibition against Gram-negative bacteria strain Klebsiella pneumoniae Carbapenem-sensible (Kpc-), Serratia marcescens, and Salmonella sp with MIC value ranging between 0.125–0.50 µg/mL.

In this study, we have found that the novel coumarylthiazole α-aminophosphonates synthesized compounds have moderate activity for antimicrobial pathogen with interesting MIC values. A modal MIC around 0.125 µg / mL relatively low and much lower than the MIC of antibiotics used in medicine: Imipenem, Ciprofloxacin, Amikacine, and Fluconazole (Fig. 2) which demonstrated an appreciable utility and leave the possibility of increasing the doses in the event of resistance provided.

Table 4 Values of MIC (μg/mL) of the synthesized α-aminophosphonates derivatives against the tested Gram-negative bacteria

	E.coli ATCC 25922	E.coli ESBL	E.coli cipro R	Kpc +	Kpc−	Kpn Sey Marseille	Serratia	Salmonella	Pseudomonas aeruginosa ATCC 27853	Pseudomenas aeruginosa (VIM-2 .1)	Pseudomenas aeruginosa (VIM-2 .2)	Acinetobacter baumanni (NDM-1)	Acinetobacter baumanni. OXA-23
(IV)a	++	0.25	0.125/32	2	4	1	1	1	1	1	8	++	++
(IV)b	0.125	0.125	0.125	32	32	0.125	0.125/128	0.125/128	0.125	0.125	0.125	++	32
(IV)c	0.125	1	0.125	8	8	4	1	1	0.125	0.125	0.125	++	16
(IV)d	0.125	0.125	64	8	16	0.125	0.125	0.125	0.125	0.125	++	++	0.125
(IV)e	0.125	0.125	++	0.125/128	0.125	0.125	0.125	0.125	0.125	0.125	++	++	0.125
(IV)f	0.125	0.125	0.25	0.5	0.125	2	8	0.125	0.125	0.125	++	++	++
(IV)g	0.125	0.125	1	++	8	0.5	1	1	1	0.125	1	++	++
(IV)h	0.125	0.125	0.5	++	++	++	0.25	0.25	0.125	0.125	0.25	++	++
(IV)i	1	1	++	16	++	++	4	4	4	4	4	16	16
(IV)j	0.125/16	4	4	0.125	0.125/128	0.125/128	0.125	0.125	0.125	2	2	128	128
(IV)k	0.5	8	8	1	32	0.125	0.125	0.5	1	4	32	++	++
(IV)l	2	4	64	0.5/8	8	1	32	2	8	16	1	++	++
(IV)m	++	8	8	–	0.5	++	0.125	0.125	2	4	2	1	1
Imipenem	–	1	5	–	–	–	–	–	–	128	64	32	32
Ciprofloxain	–	2	4	–	–	–	–	–	–	32	64	16	64
Amikacine	–	32	4	–	–	–	–	–	–	32	8	8	2

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

R resistant, *MIC* minimum inhibitory concentration

[a]Positive reference

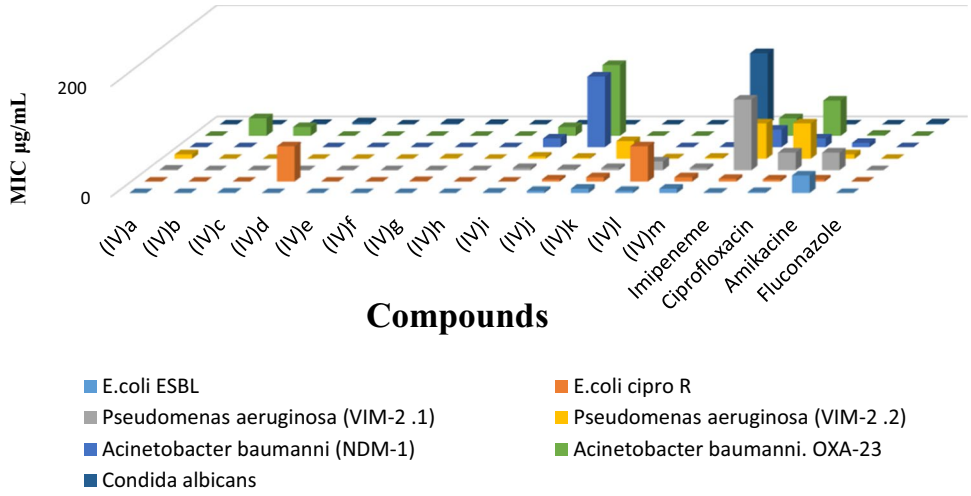


Fig. 2 Comparison of MIC values of compounds (IV)a-m with Imipenem, Ciprofloxacin, Amikacine, and Fluconazole as references.

Structure–activity relationship analysis

The structure–activity relationship (SAR) of the coumarylthiazole α-aminophosphonates derivatives presented from data of Tables 3 and 4: the best activity among all the newly synthesized compounds was exhibited with the bromine substituent derivative at the *ortho* position of the phenyl ring **(IV)e** against both antibacterial and antifungal with MIC values 0.125 µg/mL, the different substitutions at the phenyl ring were showed a high relationship increasing antibacterial activity, the electron-donating groups at *ortho* and *para* positions: 4-hydroxy-3-methoxy > 2-hydroxy > 4-methoxy increase inhibitory activities with MIC values ranging between 0.125–128 µg/mL against microbial strains. Moreover, several compounds with electron-withdrawing groups at *ortho* and *para* positions: 2-Bromo > 4-Chloro were showed strong antimicrobial activity with MIC modal of 0.125 µg/mL, the presence of nitro group (electron-withdrawing group) at *meta* position **(IV)b** showed high inhibitory activity against Gram-negative bacteria with MIC values ranging between 0.125–32 µg/mL. The heterocyclic substitutions **(IV)l** and **(IV)m** (pyrrole and chromene, respectively) showed interesting antibacterial and antifungal activities, in particular, the pyrrole derivative **(IV)l** resulted more active on some Gram-positive bacteria and Candida albicans, while the chromene derivative **(IV)m** showed better activity against some Gram-negative bacteria.

According to the SAR study, it is clear that the inhibitory effect is directly related to the type of the substituted group on the phenyl ring. Increasing antimicrobial activity depends on the presence of the α-aminophosphonates moiety and is required for a scaffold to be effective against both references and MDR strains.

Conclusion

We reported herein an efficient synthesis of thirteen coumarylthiazole α-aminophosphonates under ultrasound irradiation. All these compounds have been characterized by spectral analyses and tested for their potential antibacterial activity against Gram-positive and Gram-negative bacteria and antifungal activity against Candida Albicans by comparison with standard drugs, Imipenem, Ciprofloxacin, Amikacine, and fluconazole. We have found that the highest activity was observed by compounds **(IV)e** with MIC values of 0.125 µg/mL followed by compounds (IV)h, (IV)f, (IV)b, and (IV)d, respectively, against antimicrobial strain; thees results revealed that the inhibitory activity of the synthesized compounds could also be affected by the type of substituent on the phenyl ring. Electron-donating substituents groups especially in *ortho* and *para* positions showed quite better activities than the electron-withdrawing groups. All the synthesized compounds showed moderate and interesting antimicrobial activities and can use as new potent antimicrobial drugs for therapeutic use.

Experimental section

General

Melting points (m.p) of all the synthesized compounds were determined by the Buchi Melting Point B-545 apparatus and the values are uncorrected. Sonication was performed in a FUNGILAB ultrasonic bath with a frequency of 40 kHz and output power of 250 W. IR spectra were recorded on a PerkinElmer FT-600 spectrometer. 1H, 13C, 31 P spectra were recorded on a Bruker spectrometer 400 MHz, 101 MHz, and 162 MHz, respectively, in δ ppm using TMS as the standard. Elemental analysis (C, H, and N) was performed on a

PerkinElmer 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 a 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. The synthetic starting material, reagents, and solvents were purchased from Merck, Sigma-Aldrich, and Fluka.

Synthesis of 3-acetyl-2H-chromen-2-one (I)

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 which was washed by ether and purification by recrystallization (EtOH/$CHCl_3$) 1:3 mixture, gave 3-acetylcoumarin (I) as fine yellow needles in good yields. Isolation and spectral data of this compound were reported in the literature [43, 44].

Synthesis of 3-(2-bromoacetyl)-2H-chromen-2-one (II)

3-Acetylcoumarin (I) (10 mmol) was 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 with constant stirring at 15 min, 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, purification by recrystallization from glacial acetic acid gave 3-(bromoacetyl)-coumarin (II) as white shiny needles in good yields. Isolation and spectral data of this compound were reported in the literature [45]

Synthesis of 3-(2-amino-1,3-thiazol-4-yl)coumarin (III)

3-(2-amino-1,3-thiazol-4-yl)coumarin (III) was prepared by a mixture of Thiourea (5 mmol) and a solution of 3-(bromoacetyl)-coumarin (II) (5 mmol) in boiling ethanol (20 mL). The mixture was refluxed for 1 h, then cooled and neutralized with aqueous ammonia. The solid obtained was filtered off, washed with ethanol without recrystallization or other purification. The product was obtained in 90% yield [46].

3-(2-amino-1,3-thiazol-4-yl)coumarin: $C_{12}H_8N_2O_2S$; MW = 244.03; Yellow powder. Yield: 90%; ^{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.

Synthesis of triethyl ammonium acetate (TEAA)

Triethylammonium acetate (TEAA) has been easily prepared from the reaction of triethylamine and acetic acid according to the reported method [47]. The synthesis of TEAA was carried out in a 250-mL round-bottomed flask, which was immersed in a water-bath and fitted with a reflux condenser. (10 mmol) of Acetic acid (10 mmol) was added dropwise with constant stirring at 70 °C for 1 h. The mixture was heated at 80 °C with stirring for 2 h to ensure that the reaction had proceeded to completion. The TEAA was found in 98% yield.

General procedure for the synthesis of α-aminophosphonate-substituted coumarylthiazole (IV)a–m

In a 10-mL round-bottom flask taken a mixture of aldehyde (1 mmol) and 3-(2-amino-1,3-thiazol-4-yl)coumarin (III) (1 mmol) and TEAA (1 mL) as a catalyst at room temperature and then triethyl phosphite (1 mmol) was added. Then reaction mixture was exposed to ultrasound irradiation (US) for the appropriate time. After completion of the reaction, as indicated by TLC silica gel; dichloromethane: methanol (9.5:0.5). 5 mL of water was added to the mixture. The ionic liquid was dissolved in water and filtered for separation of the product. The separated product was washed with water. The solid product was purified by recrystallization in ethanol. Compounds (IV)a–m were obtained with 65–92% yield.

Diethyl((4-nitrophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)a Orange powder. Recrystallized from EtOH. Yield: 83%; mp: 204–205.7 °C; IR (KBr,cm^{-1}): 3383.31, 1739.41, 1520.65, 1236.76; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.96 (dd, J = 9.4, 4.4 Hz, 1H), 8.66 (s, 1H), 8.29 (d, J = 8.5 Hz, 2H), 7.88 (ddd, J = 7.8, 4.5, 1.8 Hz, 3H), 7.67 – 7.60 (m, 1H), 7.60 (s, 1H), 7.46 – 7.36 (m, 2H), 5.91 (dd, J = 22.7, 9.4 Hz, 1H), 4.20 – 3.86 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.38 (d, J_{C-P} = 11.4 Hz), 159.17, 152.70, 147.47 (d, J_{C-P} = 3.2 Hz), 144.85, 143.09, 139.14, 131.99, 129.92 (d, J_{C-P} = 5.4 Hz), 129.16, 125.14, 123.81 (d, J_{C-P} = 2.0 Hz), 120.72, 119.81, 116.31, 110.39, 63.48 (d, J_{C-P} = 6.9 Hz), 63.23 (d, J_{C-P} = 6.7 Hz), 55.79, 54.28, 16.72 (d, J_{C-P} = 5.3 Hz), 16.53 (d, J_{C-P} = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 20.05. Anal. Calcd. for

$C_{23}H_{22}N_3O_7PS$ (%): C, 53.59; H, 4.30; N, 8.15. Found: C, 54.09; H, 4.12; N, 8.36.

Diethyl((3-nitrophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)b Yellow powder. Recrystallized from EtOH. Yield: 75%; mp: 221.3–222 °C; IR (KBr,cm^{-1}): 3430.00, 1723.05, 1530.30, 1220.00; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.98 (dd, J = 9.5, 4.2 Hz, 1H), 8.71 (s, 1H), 8.58 – 8.52 (m, 1H), 8.19 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.60 (s, 1H), 7.46 – 7.37 (m, 2H), 5.94 (dd, J = 22.1, 9.4 Hz, 1H), 4.13 (ddd, J = 13.5, 9.5, 7.2 Hz, 2H), 4.07 – 3.88 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.35 (d, J_{C-P} = 11.3 Hz), 159.17, 152.72, 148.18 (d, J_{C-P} = 2.3 Hz), 143.13, 139.31 (d, J_{C-P} = 24.2 Hz), 135.45 (d, J_{C-P} = 5.5 Hz), 131.98, 130.19, 129.07, 125.15, 123.39 (d, J_{C-P} = 5.5 Hz), 123.16, 120.74, 119.85, 116.33, 110.39, 63.44 (d, J_{C-P} = 6.8 Hz), 63.19 (d, J_{C-P} = 6.7 Hz), 55.40, 53.87, 16.69 (d, J_{C-P} = 5.4 Hz), 16.51 (d, J_{C-P} = 5.6 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 20.33. Anal. Calcd. for $C_{23}H_{22}N_3O_7PS$ (%): C, 53.59; H, 4.30; N, 8.15. Found: C, 53.10; H, 4.54; N, 7.87.

Diethyl((2-nitrophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)c Brown powder. Recrystallized from EtOH. Yield: 82%; mp: 243.4–244.2 °C; IR (KBr,cm^{-1}): 3434.02, 1723.51, 1536.00, 1218.00; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.93 (dd, J = 9.1, 5.4 Hz, 1H), 8.36 (s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.2 Hz, 3H), 7.39 (dt, J = 7.5, 3.3 Hz, 2H), 6.51 (dd, J = 23.6, 9.0 Hz, 1H), 4.14 (p, J = 7.4 Hz, 2H), 4.06 – 3.83 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.53 (d, J_{C-P} = 13.7 Hz), 159.04, 152.69, 149.70 (d, J_{C-P} = 7.0 Hz), 142.95, 138.57, 134.10 (d, J_{C-P} = 2.4 Hz), 132.14 (d, J_{C-P} = 22.5 Hz), 130.03 (d, J_{C-P} = 4.0 Hz), 129.59 (d, J_{C-P} = 2.5 Hz), 128.67, 125.20 (d, J_{C-P} = 16.2 Hz), 120.69, 119.60, 116.38, 110.94, 63.63 (d, J_{C-P} = 6.9 Hz), 63.29 (d, J_{C-P} = 6.9 Hz), 50.65, 49.09, 16.71 (d, J_{C-P} = 5.1 Hz), 16.40 (d, J_{C-P} = 5.3 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 19.79. Anal. Calcd. for $C_{23}H_{22}N_3O_7PS$ (%): C, 53.59; H, 4.30; N, 8.15. Found: C, 53.27; H, 4.46; N, 7.92.

Diethyl((2-hydroxyphenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)d Yellow powder. Recrystallized from EtOH. Yield: 87%; mp: 184–188 °C; IR (KBr,cm^{-1}): 3480.00, 3246.02, 1705.08, 1543.04, 1236.04; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.62 (dd, J = 9.6, 3.5 Hz, 1H), 8.55 (s, 1H), 7.84 (dd, J = 7.7, 1.5 Hz, 1H), 7.62 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.55 (s, 1H), 7.51 – 7.33 (m, 3H), 7.16 – 7.05 (m, 1H), 6.90 – 6.72 (m, 2H), 6.06 (dd, J = 21.1, 9.6 Hz, 1H), 4.08 (dqd, J = 17.1, 7.1, 3.4 Hz, 2H), 3.99 – 3.70 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 159.17, 155.57 (d, J_{C-P} = 6.6 Hz), 152.68, 143.14, 138.68, 131.96, 129.45 (d, J_{C-P} = 4.0 Hz), 129.08, 125.16, 123.25, 121.02, 119.73, 119.32, 116.36, 115.45, 109.97, 62.85 (d, J_{C-P} = 4.9 Hz), 62.78 (d, J_{C-P} = 5.1 Hz), 49.32, 47.75, 46.15, 16.76 (d, J_{C-P} = 5.4 Hz), 16.50 (d, J_{C-P} = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 22.21. Anal. Calcd. for $C_{23}H_{23}N_2O_6PS$ (%): C, 56.79; H, 4.77; N, 5.76 Found: C, 56.68; H, 4.69; N, 5.65.

Diethyl((2-bromophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)e Yellow powder. Recrystallized from EtOH. Yield: 65%; mp: 262–263 °C; IR (KBr,cm^{-1}): 3429.48, 1722.41, 1543.33, 1233.39 ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.96 (dd, J = 9.1, 5.1, 1H), 8.68 (s, 1H), 7.77 (d, J = 7.7, 1H), 7.70 – 7.57 (m, 3H), 7.58 (d, J = 11.2, 1H), 7.47 – 7.35 (m, 3H), 7.23 (t, J = 7.7, 1H), 6.07 (dd, J = 22.3, 9.1, 1H), 4.20 – 4.08 (m, 2H), 3.91 (dp, J = 10.1, 7.2, 1H), 3.82 – 3.69 (m, 1H), 1.25 (t, J = 7.0, 3H), 1.05 (t, J = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.40 (d, J_{C-P} = 14.0 Hz), 159.10, 152.71, 143.01, 138.91, 136.84, 132.91, 132.05, 130.12 (t, J_{C-P} = 3.5 Hz), 128.94, 128.31 (d, J_{C-P} 2.9 Hz), 125.19 (d, J_{C-P} = 12.5 Hz), 120.86, 119.71, 116.37, 110.64, 63.33 (d, J_{C-P} = 6.8 Hz), 63.15 (d, J_{C-P} = 6.8 Hz), 55.43, 53.87, 16.78 (d, J_{C-P} = 5.4 Hz), 16.45 (d, J_{C-P} = 5.4 Hz). ^{31}P NMR (162 MHz, DMSO) δ 20.55. Anal. Calcd. for $C_{23}H_{22}BrN_2O_5PS$ (%): C, 50.28; H, 4.04; N, 5.10 Found: C, 50.37; H, 4.11; N, 5.17.

Diethyl((4-hydroxy-3-methoxyphenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)f Yellow powder. Recrystallized from EtOH. Yield: 73%; mp: 212–213 °C; IR (KBr,cm^{-1}): 3493.25, 3237.42, 1691.05, 1542.19, 1215.78; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.71 (s, 1H), 8.64 (dd, J = 9.7, 3.2 Hz, 1H), 7.90 (dd, J = 7.9, 1.5 Hz, 1H), 7.61 (ddd, J = 8.7, 7.3, 1.6 Hz, 1H), 7.57 (s, 1H), 7.46 – 7.35 (m, 2H), 7.22 (t, J = 1.9 Hz, 1H), 6.99 (dt, J = 8.2, 2.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 5.58 (dd, J = 21.0, 9.7 Hz, 1H), 4.17 – 3.99 (m, 2H), 3.98 – 3.73 (m, 5H), 1.19 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.67 (d, J_{C-P} = 11.4 Hz), 159.23, 152.70, 147.71, 146.67, 143.18, 138.96, 131.92, 129.14, 127.28, 125.15, 121.54 (d, J_{C-P} = 6.2 Hz), 120.85, 119.89, 116.30, 115.57, 113.49 (d, J_{C-P} = 5.5 Hz), 109.89, 62.90 (d, J_{C-P} = 4.5 Hz), 62.83 (d, J_{C-P} = 3.9 Hz), 56.21, 55.76, 54.21, 16.77 (d, J_{C-P} = 5.4 Hz), 16.58 (d, J_{C-P} = 5.7 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 21.88 (d, J = 2.9 Hz). Anal. Calcd. for $C_{24}H_{25}N_2O_7PS$ (%): C, 55.81; H, 4.88; N, 5.42 Found: C, 55.74; H, 4.72; N, 5.34.

Diethyl((3-bromophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)g White solid. Recrystallized from EtOH. Yield: 90%; mp: 215.4–216.6 °C; IR (KBr,cm^{-1}): 3427.75, 1723.27, 1540.45, 1222.12; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.80 (dd, J = 9.6, 4.0, 1H), 8.68 (s, 1H), 7.98 – 7.73 (m, 2H), 7.69 – 7.56 (m, 3H), 7.51 (d, J = 8.1, 1H), 7.39 (dt, J = 21.8, 7.8, 3H), 5.75 (dd, J = 21.9, 9.6, 1H), 4.19 – 3.82 (m, 5H), 1.15 (dt, J = 38.5, 7.1, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.43 (d, J_{C-P} = 11.3 Hz), 159.19, 152.72, 143.14, 139.61, 139.13, 131.97, 131.50 (d, J_{C-P} = 5.5 Hz), 130.99 (d, J_{C-P} = 2.7 Hz), 130.77, 129.13, 127.89 (d, J_{C-P} = 5.7 Hz), 125.15, 121.91 (d, J_{C-P} = 2.4 Hz), 120.78, 119.86, 116.32, 110.22, 63.27 (d, J_{C-P} = 7.0 Hz), 63.07 (d, J_{C-P} = 6.8 Hz), 55.47, 53.95, 16.60 (dd, J_{C-P} = 20.9 Hz, 5.4 Hz). ^{31}P NMR (162 MHz, DMSO) δ 20.76. Anal. Calcd. for $C_{23}H_{22}BrN_2O_5PS$ (%): C, 50.28; H, 4.04; N, 5.10 Found: C, 50.17; H, 3.91; N, 5.03.

Diethyl((4-chlorophenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)h White powder. Recrystallized from EtOH. Yield: 75%; mp: 193.5–194.4 °C; IR (KBr,cm^{-1}): 3491.91, 1720.44, 1539.00, 1234.45; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.79 (dd, J = 9.6, 3.9 Hz, 1H), 8.66 (s, 1H), 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.58 (s, 1H), 7.51 – 7.36 (m, 3H), 5.73 (dd, J = 22.0, 9.6 Hz, 1H), 4.15 – 4.00 (m, 2H), 4.00 – 3.82 (m, 2H), 1.19 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.51 (d, J_{C-P} = 11.5 Hz), 164.76, 159.20, 152.70, 143.13, 139.06, 135.94, 132.85 (d, J_{C-P} = 3.2 Hz), 131.96, 131.82, 130.60 (d, J_{C-P} = 5.8 Hz), 129.80, 129.19, 128.65 (d, J_{C-P} = 2.1 Hz), 125.22 (d, J_{C-P} = 19.3 Hz), 120.78, 119.84, 116.30, 110.16, 63.22 (d, J_{C-P} = 6.9 Hz), 63.02 (d, J_{C-P} = 6.8 Hz), 55.42, 53.89, 16.73 (d, J_{C-P} = 5.4 Hz), 16.53 (d, J_{C-P} = 5.5 Hz).^{31}P NMR (162 MHz, DMSO-d_6) δ 20.92. Anal. Calcd. for $C_{23}H_{22}ClN_2O_5PS$ (%): C, 54.71; H, 4.39; N, 5.55 Found: C, 54.79; H, 4.48; N, 5.61.

Diethyl(((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)(3-methoxyphenyl)methyl)phosphonate (IV)i Yellow powder. Recrystallized from EtOH. Yield: 69%; mp: 228.9–229 °C; IR (KBr,cm^{-1}): 3419.59, 1719.13, 1539.12, 1247.39; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.75 (s, 1H), 8.70 (dd, J = 9.8, 3.3, 1H), 7.83 – 7.91 (m, 1H), 7.56 – 7.66 (m, 2H), 7.35 – 7.46 (m, 2H), 6.97 (d, J = 1.9, 2H), 5.64 (dd, J = 21.2, 9.7, 1H), 3.81 – 4.18 (m, 4H), 3.31 (s, 3H), 1.21 (t, J = 7.0, 3H), 1.10 (t, J = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.61 (d, J_{C-P} = 11.3 Hz), 159.21, 153.04 (d, J_{C-P} = 2.0 Hz), 152.72, 143.18, 139.06, 132.07 (d, J_{C-P} = 25.4 Hz), 129.04, 125.18, 120.83, 119.91, 116.33, 110.03, 106.65 (d, J_{C-P} = 5.9 Hz), 62.98 (t, J_{C-P} = 6.5 Hz), 60.46 (d, J_{C-P} = 1.6 Hz), 56.48, 16.78 (d, J_{C-P} = 5.3 Hz), 16.56 (d, J_{C-P} = 5.6 Hz). ^{31}P NMR (162 MHz, DMSO) δ 21.39. Anal. Calcd. for $C_{24}H_{25}N_2O_6PS$ (%): C, 57.59; H, 5.03; N, 5.60 Found: C, 57.48; H, 5.04; N, 5.52.

Diethyl((4-methoxyphenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)j Yellow powder. Recrystallized from EtOH. Yield: 76%; mp: 236.8–237 °C; IR (KBr,cm^{-1}): 3418.48, 1716.49, 1543.33, 1233.39; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.72 (dd, J = 9.8, 3.4 Hz, 1H), 8.69 (s, 1H), 7.95 – 7.88 (m, 1H), 7.61 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.57 (s, 1H), 7.55 – 7.50 (m, 2H), 7.46 – 7.35 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.65 (dd, J = 21.3, 9.7 Hz, 1H), 4.16 – 3.99 (m, 2H), 3.95 (ddt, J = 17.4, 14.3, 6.7 Hz, 1H), 3.89 – 3.76 (m, 1H), 3.74 (s, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.63 (d, J_{C-P} = 11.4 Hz), 159.27, 159.24, 159.22, 152.69, 143.15, 138.97, 131.93, 130.06 (d, J_{C-P} = 5.9 Hz), 129.23, 125.12, 120.81, 119.86, 116.29, 114.06, 109.96, 62.96 (d, J_{C-P} = 6.9 Hz), 62.83 (d, J_{C-P} = 6.8 Hz), 55.54, 55.31, 53.77, 16.76 (d, J_{C-P} = 5.2 Hz), 16.56 (d, J_{C-P} = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 21.78. Anal. Calcd. for $C_{24}H_{25}N_2O_6PS$ (%): C, 57.59; H, 5.03; N, 5.60 Found: C, 57.65; H, 5.13; N, 5.67.

Diethyl((4-(dimethylamino)phenyl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)k Brown powder. Recrystallized from EtOH. Yield: 65%; mp: 207.1–208.3 °C; IR (KBr,cm^{-1}): 3422.00, 1723.21, 1541.27, 1216.59; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.67 (s, 1H), 8.60 (dd, J = 9.8, 3.2, 1H), 7.96 – 7.89 (m, 1H), 7.66 – 7.53 (m, 2H), 7.46 – 7.35 (m, 4H), 6.71 (d, J = 8.4, 2H), 5.55 (dd, J = 21.1, 9.7, 1H), 4.06 (ddd, J = 16.6, 9.7, 6.9, 2H), 3.93 (dt, J = 10.2, 7.1, 1H), 3.87 – 3.72 (m, 1H), 3.33 (s, 1H), 2.87 (s, 6H), 1.18 (t, J = 7.0, 3H), 1.08 (t, J = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 166.74 (d, J_{C-P} = 11.5 Hz), 159.23, 152.68, 150.39, 143.15, 138.88, 131.92, 129.58 (d, J_{C-P} = 6.0 Hz), 129.26, 125.12, 123.64, 120.86, 119.87, 116.28, 112.37, 109.82, 62.77 (dd, J_{C-P} = 9.7 Hz, 6.8 Hz), 55.44, 53.88, 16.78 (d, J_{C-P} = 5.3 Hz), 16.60 (d, J_{C-P} = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO) δ 22.12. Anal. Calcd. for $C_{25}H_{28}N_3O_5PS$ (%): C, 58.47; H, 5.50; N, 8.18 Found: 58.54; H, 5.59; N, 8.25.

Diethyl(((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)(1H-pyrrol-2-yl)methyl)phosphonate (IV)l Red solid. Recrystallized from EtOH. Yield: 91%; mp: 210.5–211.4 °C; IR (KBr,cm^{-1}): 3432.87, 1723.99, 1537.69, 1231.70; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.75 (s, 1H), 8.71 (s, 1H), 8.40 (dd, J = 9.5, 2.0, 1H), 7.85 (dd, J = 7.7, 1.6, 1H), 7.62 (ddd, J = 8.7, 7.3, 1.6, 1H), 7.58 (s, 1H), 7.47 – 7.34 (m, 2H), 6.72 (dq, J = 2.6, 1.3, 1H), 6.21 (dq, J = 4.0, 2.1, 1H), 6.01 (q, J = 2.8, 1H), 5.72 (dd, J = 20.5, 9.5, 1H), 4.16 – 3.75 (m, 3H), 1.18 (t, J = 7.0, 3H), 1.08 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.72

(d, J_{C-P} = 9.4 Hz), 159.23, 152.70, 143.15, 138.89, 131.94, 129.02, 125.80 (d, J_{C-P} = 2.5 Hz), 125.20, 120.88, 119.85, 118.10 (d, J_{C-P} = 2.1 Hz), 116.35, 109.92, 108.17, 107.78 (d, J_{C-P} = 4.9 Hz), 62.95 (d, J_{C-P} = 6.8 Hz), 50.19, 48.59, 16.74 (d, J_{C-P} = 5.3 Hz), 16.57 (d, J = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO-d_6) δ 20.65. Anal. Calcd. for $C_{21}H_{22}N_3O_5PS$ (%): C, 54.90; H, 4.83; N, 9.15 Found: C, 54.79; H, 4.75; N, 9.09.

Diethyl((4H-chromen-3-yl)((5-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)amino)methyl)phosphonate (IV)m Dark brown solid. Recrystallized from EtOH. Yield: 92%; mp: 213.1–214.2 °C; IR (KBr,cm^{-1}): 3450.00, 1722.74, 1539.01, 1218.00; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.57 – 8.49 (m, 3H), 8.19 (dd, J = 8.0, 1.7, 1H), 7.82 (tdd, J = 8.6, 7.3, 1.7, 2H), 7.67 (dd, J = 8.6, 1.0, 1H), 7.65 – 7.57 (m, 2H), 7.54 (ddd, J = 8.1, 7.1, 1.1, 1H), 7.46 – 7.35 (m, 2H), 5.91 (dd, J = 20.5, 9.2, 1H), 4.26 – 3.96 (m, 4H), 1.24 (t, J = 7.0, 3H), 1.15 (t, J = 7.0, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 175.00 (d, J_{C-P} = 4.5 Hz), 166.45 (d, J_{C-P} = 10.6 Hz), 159.13, 156.09 (d, J_{C-P} = 7.1 Hz), 152.69, 143.22, 138.73, 135.01, 132.02, 128.95, 126.40, 125.27, 123.36, 120.97 (d, J_{C-P} = 8.1 Hz), 119.70, 119.02, 116.37, 63.44 (d, J_{C-P} = 6.8 Hz), 63.10 (d, J_{C-P} = 6.9 Hz), 46.78, 45.19, 16.73 (d, J_{C-P} = 5.4 Hz), 16.61 (d, J_{C-P} = 5.5 Hz). ^{31}P NMR (162 MHz, DMSO) δ 21.00. Anal. Calcd. for $C_{26}H_{25}N_2O_6PS$ (%): C, 59.54; H, 4.80; N, 5.34 Found: C, 59.62; H, 4.87; N, 5.41.

Pharmacological/biological assays

Antimicrobial activity of all pure compounds was screened for in vitro antibacterial activity in terms of MIC values against five Gram-positive bacteria: Bacillus cereus, Staphylococcus aureus ATCC25900, Staphylococcus aureus ATCC25923, Staphylococcus aureus ATCC 29213, Enterococcus faecalis resistant for vancomycine, and thirteen Gram-negative bacteria: Escherichia coli ATCC 25922, Escherichia coli ESBL (enlarged spectre β-lactamase), Escherichia coli resistant for ciprofloxacine, Klebsiella pneumoniae Carbapenem-resistant (Kpc +), Klebsiella pneumoniae Carbapenem-sensible (Kpc-), Klebsiella pneumoniae Sey Marseille, Serratia marcescens, Salmonella sp, Pseudomonas aeruginosa ATCC 27853, Pseudomonas aeruginosa imipenem-resistant (VIM-2.1), Pseudomonas aeruginosa imipenem-resistant (VIM-2.2), Acinetobacter baumanni (NDM-1), Acinetobacter baumanni. OXA-23 and a fungal strain Candida albicans. All of them were isolated from patients hospitalized in the various departments at Annaba hospital-Algeria. Their identification and susceptibility profile is reported by Toumi et al. [48] and Meliani et al. [49]. 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 minimum inhibition concentration (MIC) of the compounds was determined by broth micro-dilution method used DMSO in µg/mL [50]. And the microbial suspensions were prepared in Muller-Hinton broth from test organisms sub-cultured on nutrient agar and incubated at 37 °C for24 h.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11030-021-10242-2.

Acknowledgements This study is supported by the General Directorate for Scientific Research and Technological Development (DG-RSDT), Algerian Ministry of Scientific Research, Algeria. We are grateful to CRAPC SPA Expertise for recording elemental analyses and NMR spectra.

References

1. Interagency Coordination Group on Antimicrobial Resistance (2019) No time to wait: securing the future from drug-resistant infections. Report to the secretary-general of the United Nations. IACG, p 28
2. Parvaiz N, Ahmad F, Yu W, MacKerell AD Jr, Azam SS (2021) Discovery of beta-lactamase CMY-10 inhibitors for combination therapy against multi-drug resistant Enterobacteriaceae. PLoS ONE 16(1):e0244967. https://doi.org/10.1371/journal.pone.0244967
3. Hassan AE, Moustafa AH, Tolbah MM, Zohdy HF, Haikal AZ (2012) Synthesis and antimicrobial evaluation of novel pyrazolones and pyrazolone nucleosides. Nucl Nucl Nucl Acids 31:783–800. https://doi.org/10.1080/15257770.2012.732250
4. Santoro AM, Lanza V, Bellia F, Sbardella D, Tundo GR, Cannizzo A, Grasso G, Arizzi M, Nicoletti VG, Alcaro S (2020) Pyrazolones activate the proteasome by gating mechanisms and protect neuronal cells from β-amyloid toxicity. Chem Med Chem 15:302–316. https://doi.org/10.1002/cmdc.201900612
5. Kakkar S, Tahlan S, Lim SM, Ramasamy K, Mani V, Shah SAA, Narasimhan B (2018) Benzoxazole derivatives: design, synthesis and biological evaluation. Chem Cent J 12(92):1–16. https://doi.org/10.1080/15257770.2014.891742
6. Nagesh N, Raju G, Srinivas R, Ramesh P, Reddy MD, Reddy CR (2015) A dihydroindolizino indole derivative selectively stabilizes G-quadruplex DNA and down-regulates c-MYC expression in human cancer cells. Biochem Biophys Acta 1850:129–140. https://doi.org/10.1080/15257770.2014.891742
7. Raju G, Srinivas R, Reddy MD, Reddy ChR, Nagesh N (2014) Studies on non-covalent interaction of coumarin attached pyrimidine and 1-methyl indole 1,2,3 triazole analogues with intermolecular telomeric G-quadruplex DNA using ESI-MS and spectroscopy. Nucl Nucl Nucl Acids 33(7):489–506. https://doi.org/10.1080/15257770.2014.891742
8. Nayak S, Gaonkar SL (2019) A review on recent synthetic strategies and pharmacological importance of 1, 3-thiazole derivatives. Mini Rev Med Chem 19:215–238. https://doi.org/10.2174/1389557518666180816112151
9. Rouf A, Tanyeli C (2015) Bioactive thiazole and benzothiazole derivatives. Eur J Med Chem 97:911–927. https://doi.org/10.1016/j.ejmech.2014.10.058
10. Gore VA, Tekale SU, Bhale SP, Rajani DP, Domb AJ, Pawar RP (2021) Synthesis and biological evaluation of novel thiazole hydrazines as antimicrobial and antimalarial agents. Lett Appl Nano Biosci 10:1846–1855. https://doi.org/10.33263/LIANBS101.18461855

11. Ghotbi G, Mahdavi M, Najafi Z (2020) Design, synthesis, biological evaluation, and docking study of novel dual-acting thiazole-pyridiniums inhibiting acetylcholinesterase and β-amyloid aggregation for Alzheimer's disease. Bioorg Chem 103:104186. https://doi.org/10.1016/j.bioorg.2020.104186
12. Coman FM, Mbaveng AT, Marc G, Leonte D, Brém B, Vlase L, Imre S, Kuete V, Zaharia V (2020) Synthesis, characterization and biological evaluation of some new thiazole aurones as antiproliferative agents. Farmacia 68(3):492–506. https://doi.org/10.31925/farmacia.2020.3.1
13. Sundaree S, Vaddula BR, Tantak MP, Khandagale SB, Shi C, Shah K, Kumar D (2016) Synthesis and anticancer activity study of indolyl hydrazidehydrazones. Med Chem Res 25:941–950. https://doi.org/10.1007/s00044-016-1522-1
14. Khan B, Naiyer A, Athar F, Ali S, Thakur SC (2019) Synthesis, characterization and anti-inflammatory activity evaluation of 1, 2, 4-triazole and its derivatives as a potential scaffold for the synthesis of drugs against prostaglandin-endoperoxide synthase. J Biomol Struct Dyn 10:1–19. https://doi.org/10.1080/07391102.2019.1711193
15. Ibrar A, Shehzadi SA, Saeed F, Khan I (2018) Developing hybrid molecule therapeutics for diverse enzyme inhibitory action: active role of coumarin-based structural leads in drug discovery. Bioorg Med Chem 26:3731–3762. https://doi.org/10.1016/j.bmc.2018.05.042
16. Singh H, Singh JV, Bhagat K, Gulati HK, Sanduja M, Kumar N, Kinarivala N, Sharma S (2019) Rational approaches, design strategies, structure activity relationship and mechanistic insights for therapeutic coumarin hybrids. Bioorg Med Chem 27:3477–3510. https://doi.org/10.1016/j.bmc.2019.06.033
17. Khaled RA, Mohamed AA, Heba AH, Nesma MK, Dalia ME (2017) Design, synthesis, antioxidant and anticancer activity of new coumarin derivatives linked with thiazole, isoxazole or pyrazole moiety. Lett Drug Des Discov 14:773–781. https://doi.org/10.2174/1570180813666161026153743
18. You-Xian W, Shu-Hao Z-B, Lian-Gong K-J, Xing L, Lei W, Wei-Wei L, Da-Hua S, Zhi-Ling C (2020) Synthesis and anti-acetylcholinesterase activities of novel glycosyl coumarylthiazole derivatives. J Chem Res. https://doi.org/10.1177/1747519820948358
19. Kalkhambkar R, Kulkarni G, Shivkumar H, Rao R (2007) Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents. Eur J Med Chem 42:1272. https://doi.org/10.1016/j.ejmech.2007.01.023
20. KhanY S, Osman H, Khan MS, Mohamad S, Sulaiman O, Parumasivam T, Gansau JA, Johansah N (2017) Design, characterization, in vitro antibacterial, antitubercular evaluation and structure—activity relationships of new hydrazinyl thiazolyl coumarin derivatives. Med Chem Res 26(6):1139–1148. https://doi.org/10.1007/s00044-017-1820-2
21. Zengin-Kurt B, Gazioglu I, Sonmez F, Kucukislamoglu M (2015) Synthesis, antioxidant and anticholinesterase activities of novel coumarylthiazole derivatives. Bioorg Chem 59:80–90. https://doi.org/10.3109/14756366.2015.1077823
22. Zengin-Kurt B, Sonmez F, Gokce B (2016) In vitro inhibition effects on erythrocyte carbonic anhydrase I and II and structure-activity relationships of cumarylthiazole derivatives. Russ J Bioorg Chem 42:506–511. https://doi.org/10.1134/S1068162016050046
23. Azzam MA, El-Boraey HL, El-Sayed IE (2020) Transition metal complexes of α-aminophosphonates part II: synthesis, spectroscopic characterization, and in vitro anticancer activity of copper(II) complexes of α-aminophosphonates. Phosphorus Sulfur Silicon Relat Elem 195(4):339–347. https://doi.org/10.1080/10426507.2019.1700258
24. Maestro A, Marigorta EM, Palacios F, Vicario J (2020) α-Iminophosphonates: Useful intermediates for enantioselective synthesis of α-aminophosphonates. Asian J Org Chem 9:538–548. https://doi.org/10.1002/ajoc.202000039
25. Shaikh S, Dhavan P, Pavale G, Ramana MM, Jadhav BL (2020) Design, synthesis and evaluation of pyrazole bearing α-aminophosphonate derivatives as potential acetylcholinesterase inhibitors against Alzheimer's disease. Bioorg Chem 96:103589. https://doi.org/10.1016/j.bioorg.2020.103589
26. An TN, Cuong NV, Quang NM, Thanh TV, Alam M (2020) Green synthesis using PEG-400 catalyst, antimicrobial activities, cytotoxicity and in silico molecular docking of new carbazole based on α-aminophosphonate. ChemistrySelect 5:6339. https://doi.org/10.1002/slct.202000855
27. Harika P, Abbo HS, Krishna Murthy P (2019) Polyethylene glycol (PEG-400): an efficient one-pot green synthesis and anti-viral activity of novel *α*-Diaminophosphonates. Phosphorus Sulfur Silicon Relat Elem 194(11):1035–1039. https://doi.org/10.1080/10426507.2019.1597365
28. Rasool SK, Suresh M, Krishna Murthy P (2020) *In silico* molecular docking and in vitro antioxidant activity studies of novel *α*-Aminophosphonates bearing 6-amino-1,3-dimethyluracil. J Recept Sig Transd 40(2):166–172. https://doi.org/10.1080/10799893.2020.1722166
29. Prasad GS, Rao GN (2013) Synthesis of biologically active α-aminophosphonates. J Mod Med Chem 1:49–60. https://doi.org/10.12970/2308-8044.2013.01.01.5
30. Gao G, Chen MN, Mo LP, Zhang ZH (2019) Catalyst Free One-Pot Synthesis of α-Aminophosphonates in Aqueous Ethyl Lactate. Phosphorus, Sulfur Silicon Relat. Elem 194: 528–532. https://doi.org/10.1080/10426507.2018.1542395.
31. Bedolla-Medrano M, Hernández-Fernández E, Ordóñez M (2014) Phenylphosphonic acid as efficient and recyclable catalyst in the synthesis of α-aminophosphonates under solvent-free conditions. Synlett 25:1145–1149. https://doi.org/10.1055/s-0033-1341069
32. Sun GY, Hou JT, Dou JJ, Lu J, Hou YJ, Xue T, Zhang ZH (2010) Xanthan sulfuric acid as an efficient biodegradable and recyclable catalyst for the one-pot synthesis of α-amino phosphonates. J Chin Chem Soc 57:1315–1320. https://doi.org/10.1002/jccs.201000194
33. Gallardo-Macias R, Nakayama K (2010) Tin(II) compounds as catalysts for the Kabachnik–Fields reaction under solvent-free conditions: Facile synthesis of α-aminophosphonates. Synthesis 1:57–62. https://doi.org/10.1055/s-0029-1217091
34. Hosseini-Sarvari M (2008) TiO_2 as a new and reusable catalyst for one-pot threecomponent syntheses of α-aminophosphonates in solvent-free conditions. Tetrahedron 64:5459–5466. https://doi.org/10.1016/j.tet.2008.04.016
35. Rezaei Z, Firouzabadi H, Iranpoor N, Ghaderi A, Jafari MR, Zare HR (2009) Design and one-pot synthesis of α-aminophosphonates and bis(α-aminophosphonates) by iron(III) chloride and cytotoxic activity. Eur J Med Chem 44:4266–4275. https://doi.org/10.1016/j.ejmech.2009.07.009
36. Bhattacharya AK, Rana KC (2008) Amberlite-IR 120 catalyzed threecomponent synthesis of α-aminophosphonates in one-pot. Tetrahedron Lett 49:2598–2601. https://doi.org/10.1016/j.tetlet.2008.02.102
37. Tang J, Wang L, Wang W, Zhang L, Wu S, Mao D (2011) A facile synthesis of α-aminophosphonates catalyzed by ytterbium perfluorooctanoate under solvent-free conditions. J Fluor Chem 132:102–106. https://doi.org/10.1016/j.jfluchem.2010.12.002
38. Ambica KS, Taneja SC, Hundal MS, Kapoor KK (2008) Onepot synthesis of α-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina. Tetrahedron Lett 49:2208–2212. https://doi.org/10.1016/j.tetlet.2008.02.047

39. Akiyama T, Sanada M, Fuchibe K (2003) Bronsted acid-mediated synthesis of α-amino phosphonates under solventfree conditions. Synlett 2003:1463–1464. https://doi.org/10.1055/s-2003-40858
40. Rasal SA, Tamore MS, Shimpi NG (2019) Ultrasoundmediated synthesis of novel α-aminophosphonates using graphene nanosheets-silver nanoparticles (GNS-AgNPs) as a recyclable heterogeneous catalyst. ChemistrySelect 4(8):2293–2300. https://doi.org/10.1002/slct.201803201
41. Shankar B, Jalapathi P, Nagamani M, Bharath G, Karunakarrao K (2017) Synthesis, anti-microbial activity, and cytotoxicity of novel 1-[5-[6-[(2-benzoylbenzofuran-5-yl)methyl]-2-oxo-2*H*-chromen-3-yl]thiazol-2-yl]urea derivatives. Monatshefte Chem Chem Mon 148:999–1009. https://doi.org/10.1007/s00706-016-1838-z
42. Bazine I, Bendjedid S, Boukhari A (2020) Potential antibacterial and antifungal activities of novel sulfamidophosphonate derivatives bearing the quinoline or quinolone moiety. Arch Pharm 354:e2000291. https://doi.org/10.1002/ardp.202000291
43. KhanYusufzai S, Osman H, Khan MS, Mohamad S, Sulaiman O, Parumasivam T, Gansau JA, Johansah N (2017) Design, characterization, in vitro antibacterial, antitubercular evaluation and structure–activity relationships of new hydrazinyl thiazolyl coumarin derivatives. Med Chem Res 26(6):1139–1148. https://doi.org/10.1007/s00044-017-1820-2
44. Karade N, Gampawar SN, Shinde SV, Jadhav WN (2007) L-Proline catalyzed solvent-free Knoevenagel condensation for the synthesis of 3-substituted coumarins. Chin J Chem 25:1686–1689. https://doi.org/10.1002/cjoc.200790311
45. Ingale N, Maddi V, Palkar M (2012) Synthesis and evaluation of anti-inflammatory and analgesic activity of 3-[(5-substituted1,3,4-oxadiazol-2-yl-thio)acetyl]-2H-chromen-2-ones. Med Chem Res 21:16–26. https://doi.org/10.1007/s00044-010-9494-z
46. Zhuravel OI, Kovalenko SM, Vlasov SV, Chernykh VP (2005) Solutionphase synthesis of a combinatorial library of 3-[4-(coumarin-3-yl)-1,3-thiazol-2-ylcarbamoyl]propanoic acid amides. Molecules 10:444–456. https://doi.org/10.3390/10020444
47. Balaskar RS, Gavande SN, Mane MS, Shingate BB, Shingare MS, Mane DV (2010) Greener approach towards the facile synthesis of 1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanide derivatives at room temperature. Chin Chem Lett 21(10):1175–1179. https://doi.org/10.1016/j.cclet.2010.06.013
48. Toumi S, Meliani S, Amoura K, Racherache A, Djebien M, Djahoudi A (2018) Multidrug-resistant Gram-negative bacilli producing oxacillinases and Metallo-β-lactamases isolated from patients in intensive care unit-Annaba hospital-Algeria (2014–2016). J Appl Pharm Sci 8:107–113. https://doi.org/10.7324/JAPS.2018.8717
49. Meliani S, Toumi S, Djahoudi H, Deghdegh K, Amoura K, Djahoudi A (2020) Synergistic combination of colistin with imipenem, amikacine or ciprofloxacin against Acinetobacter baumannii and Pseudomonas aeruginosa carbapenem-resistant isolated in Annaba hospital Algeria. Biocell 44(2):175–182. https://doi.org/10.32604/biocell.2020.09097
50. National Committee for Clinical Laboratory Standards, NCCLS document M27-A2, National Committee for Clinical Laboratory Standards (2002) Wayne, PA, US

Authors and Affiliations

Bilal Litim[1] · Zinelaabidine Cheraiet[2] · Saida Meliani[3] · Abdelghani Djahoudi[4] · Abbes Boukhari[1]

[1] Laboratory of Organic Synthesis, Modeling and Optimization of Chemical Processes, Department of Chemistry, Faculty of Sciences, Badji Mokhtar-Annaba University, BP 12, 23000 Annaba, Algeria

[2] Laboratory of Organic Synthesis, Modeling and Optimization of Chemical Processes, Faculty of Exact Sciences and Natural and Life Sciences, Larbi Tebeessi-Tebessa University, 12002 Tebessa , Algeria

[3] Laboratory of Microbiology, Department of Biochemistry, Faculty of Sciences, Badji Mokhtar-Annaba University, BP 205, Annaba, Algeria

[4] Laboratory of Microbiology, Department of Pharmacy, Faculty of Medicine, Badji Mokhtar-Annaba University, BP 205, Annaba, Algeria