Supplementary Material

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

Medicinal Chemistry Research

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List of figures

Fig. 1 $^1$H NMR spectrum of (3)
Fig. 2 $^{13}$C NMR spectrum of (3)
Fig. 3 HSQC 2D NMR spectrum of (3)
Fig. 4 HMBC 2D NMR spectrum of (3)
Fig. 5 $^1$H NMR spectrum of (6b)
Fig. 6 $^{13}$C NMR spectrum of (6b)
Fig. 7 HSQC 2D NMR spectrum of (6b)
Fig. 8 HMBC 2D NMR spectrum of (6b)
Fig. 9 $^1$H NMR spectrum of (7c)
Fig. 10 $^{13}$C NMR spectrum of (7c)
Fig. 11 HSQC 2D NMR spectrum of (7c)
Fig. 12 HMBC 2D NMR spectrum of (7c)
Fig. 13 $^1$H NMR spectrum of (8b)
Fig. 14 $^{13}$C NMR spectrum of (8b)
Fig. 15 HSQC 2D NMR spectrum of (8b)
Fig. 16 HMBC 2D NMR spectrum of (8b)
Fig. 17 $^1$H NMR spectrum of (9)a
Fig. 18 $^{13}$C NMR spectrum of 9a
Fig. 19 $^{31}$P NMR spectrum of 9a
Fig. 20 HSQC 2D NMR spectrum of 9a

Fig. 21 HMBC 2D NMR spectrum of 9a

Fig. 22 $^1$H NMR spectrum of 9b

Fig. 23 $^{13}$C NMR spectrum of 9b

Fig. 24 $^{31}$P NMR spectrum of 9b

Fig. 25 HSQC 2D NMR spectrum of 9b

Fig. 26 HMBC 2D NMR spectrum of 9b

Fig. 27 $^1$H NMR spectrum of 9c

Fig. 28 $^{13}$C NMR spectrum of 9c

Fig. 29 $^{31}$P NMR spectrum of 9c

Fig. 30 HSQC 2D NMR spectrum of 9c

Fig. 31 HMBC 2D NMR spectrum of 9c

Fig. 32 $^1$H NMR spectrum of 9d

Fig. 33 $^{13}$C NMR spectrum of 9d

Fig. 34 $^{31}$P NMR spectrum of 9d

Fig. 35 HSQC 2D NMR spectrum of 9d

Fig. 36 HMBC 2D NMR spectrum of 9d

Fig. 37 $^1$H NMR spectrum of 9e

Fig. 38 $^{13}$C NMR spectrum of 9e

Fig. 39 $^{31}$P NMR spectrum of 9e
Fig. 40  HSQC 2D NMR spectrum of 9e
Fig. 41  HMBC 2D NMR spectrum of 9e
Fig. 42  $^1$H NMR spectrum of 9f
Fig. 43  $^{13}$C NMR spectrum of 9f
Fig. 44  $^{31}$P NMR spectrum of 9f
Fig. 45  HSQC 2D NMR spectrum of 9f
Fig. 46  HMBC 2D NMR spectrum of 9f
Fig. 47  $^1$H NMR spectrum of 9g
Fig. 48  $^{13}$C NMR spectrum of 9g
Fig. 49  $^{31}$P NMR spectrum of 9g
Fig. 50  HSQC 2D NMR spectrum of 9g
Fig. 51  HMBC 2D NMR spectrum of 9g
Fig. 52  $^1$H NMR spectrum of 9h
Fig. 53  $^{13}$C NMR spectrum of 9h
Fig. 54  $^{31}$P NMR spectrum of 9h
Fig. 55  HSQC 2D NMR spectrum of 9h
Fig. 56  HMBC 2D NMR spectrum of 9h
Fig. 57  $^1$H NMR spectrum of 10i
Fig. 58  $^{13}$C NMR spectrum of 10i
Fig. 59  $^{31}$P NMR spectrum of 10i
Fig. 60 HSQC 2D NMR spectrum of 10i

Fig. 61 HMBC 2D NMR spectrum of 10i

Fig. 62 $^1$H NMR spectrum of 10j

Fig. 63 $^{13}$C NMR spectrum of 10j

Fig. 64 $^{31}$P NMR spectrum of 10j

Fig. 65 HSQC 2D NMR spectrum of 10j

Fig. 66 HMBC 2D NMR spectrum of 10j

Fig. 67 $^1$H NMR spectrum of 10k

Fig. 68 $^{13}$C NMR spectrum of 10k

Fig. 69 $^{31}$P NMR spectrum of 10k

Fig. 70 HSQC 2D NMR spectrum of 10k

Fig. 71 HMBC 2D NMR spectrum of 10k

Fig. 72 $^1$H NMR spectrum of 10l

Fig. 73 $^{13}$C NMR spectrum of 10l

Fig. 74 $^{31}$P NMR spectrum of 10l

Fig. 75 HSQC 2D NMR spectrum of 10l

Fig. 76 HMBC 2D NMR spectrum of 10l
Fig. 1 $^1$H NMR spectrum of (3)

Fig. 2 $^{31}$C NMR spectrum of (3)
Fig. 3 HSQC 2D NMR spectrum of (3)

Fig. 4 HMBC 2D NMR spectrum of (3)
Fig. 5 $^1$H NMR spectrum of (6b)
Fig. 6 $^{13}$C NMR spectrum of (6b)

Fig. 7 HSQC 2D NMR spectrum of (6b)
Fig. 8 HMBC 2D NMR spectrum of (6b)

Fig. 9 $^1$H NMR spectrum of (7c)
Fig. 10 $^{13}$C NMR spectrum of (7c)

Fig. 11 HSQC 2D NMR spectrum of (7c)
Fig. 12 HMBC 2D NMR spectrum of (7c)

Fig. 13 $^1$H NMR spectrum of (8b)
Fig. 14 $^{13}$C NMR spectrum of (8b)

Fig. 15 HSQC 2D NMR spectrum of (8b)
Fig. 16 HMBC 2D NMR spectrum of (8b)

Fig. 17 $^1$H NMR spectrum of 9a
Fig. 18 $^{13}$C NMR spectrum of 9a

Fig. 19 $^{31}$P NMR spectrum of 9a
**Fig. 20** HSQC 2D NMR spectrum of 9a

**Fig. 21** HMBC 2D NMR spectrum of 9a
Fig. 22 $^1$H NMR spectrum of 9b

Fig. 23 $^{13}$C NMR spectrum of 9b
Fig. 24 $^{31}$P NMR spectrum of 9b

Fig. 25 HSQC 2D NMR spectrum of 9b
Fig. 26 HMBC 2D NMR spectrum of 9b

Fig. 27 $^1$H NMR spectrum of 9c
Fig. 28 $^{13}$C NMR spectrum of 9c

Fig. 29 $^{31}$P NMR spectrum of 9c
Fig. 30 HSQC 2D NMR spectrum of 9c

Fig. 31 HMBC 2D NMR spectrum of 9c
Fig. 32 $^1$H NMR spectrum of 9d

Fig. 33 $^{13}$C NMR spectrum of 9d
**Fig. 34** $^{31}$P NMR spectrum of 9d

**Fig. 35** HSQC 2D NMR spectrum of 9d
Fig. 36 HMBC 2D NMR spectrum of 9d

Fig. 37 $^1$H NMR spectrum of 9e
Fig. 38 $^{13}$C NMR spectrum of 9e

Fig. 39 $^{31}$P NMR spectrum of 9e
Fig. 40 HSQC 2D NMR spectrum of 9e

Fig. 41 HMBC 2D NMR spectrum of 9e
Fig. 42 $^1$H NMR spectrum of 9f

Fig. 43 $^{13}$C NMR spectrum of 9f
Fig. 44 $^{31}$P NMR spectrum of 9f

Fig. 45 HSQC 2D NMR spectrum of 9f
Fig. 46 HMBC 2D NMR spectrum of 9f

Fig. 47 $^1$H NMR spectrum of 9g
Fig. 48 $^{13}$C NMR spectrum of 9g

Fig. 49 $^{31}$P NMR spectrum of 9g
Fig. 50 HSQC 2D NMR spectrum of 9g

Fig. 51 HMBC 2D NMR spectrum of 9g
**Fig. 52** $^1$H NMR spectrum of 9h

**Fig. 53** $^{13}$C NMR spectrum of 9h

**Fig. 54** $^{31}$P NMR spectrum of 9h
Fig. 55 HSQC 2D NMR spectrum of 9h

Fig. 56 HMBC 2D NMR spectrum of 9h
Fig. 57 $^1$H NMR spectrum of 10i

Fig. 58 $^{13}$C NMR spectrum of 10i
Fig. 59 $^{31}$P NMR spectrum of 10i

Fig. 60 HSQC 2D NMR spectrum of 10i
**Fig. 61** HMBC 2D NMR spectrum of 10i

**Fig. 62** $^1$H NMR spectrum of 10j
Fig. 63 $^{13}$C NMR spectrum of 10j

Fig. 64 $^{31}$P NMR spectrum of 10j
Fig. 65 HSQC 2D NMR spectrum of 10j

Fig. 66 HMBC 2D NMR spectrum of 10j
Fig. 67 $^1$H NMR spectrum of 10k

Fig. 68 $^{13}$C NMR spectrum of 10k
Fig. 69 $^{31}$P NMR spectrum of 10k

Fig. 70 HSQC 2D NMR spectrum of 10k
Fig. 71 HMBC 2D NMR spectrum of 10k

Fig. 72 $^1$H NMR spectrum of 10l
Fig. 73 $^{13}$C NMR spectrum of 10l

Fig. 74 $^{31}$P NMR spectrum of 10l
Fig. 75 HSQC 2D NMR spectrum of 10l

Fig. 76 HMBC 2D NMR spectrum of 10l
Dr. Francisco Leon 15/10/2021

Editor-in-Chief, Medicinal Chemistry Research

Resubmission of manuscript: Synthesis and potential antimicrobial activity of novel α-aminophosphonates derivatives bearing substituted quinoline or quinolone and thiazole moieties, MCRE-D-21-00781R2

Dear Editor

We would like to thank you for the letter dated 05/10/2021, and the opportunity to resubmit a revised copy of this manuscript. We would also like to take this opportunity to express our thanks to the reviewers for the positive feedback and helpful comments for correction or modification.

We believe have resulted in an improved revised manuscript, which you will find uploaded alongside this document. The manuscript has been revised to address the reviewer comments, which are appended alongside our responses to this letter.

We very much hope the revised manuscript is accepted for publication in Medicinal Chemistry Research.

Sincerely yours,

Dr. Bilal Litim
Dear Editors:

Thank you for the opportunity to revise our manuscript, Synthesis and potential antimicrobial activity of novel α-aminophosphonates derivatives bearing substituted quinoline or quinolone and thiazole moieties. We appreciate the careful review and constructive suggestions. It is our belief that the manuscript is substantially improved after making the suggested edits. The revision has been developed in consultation with all coauthors, and each author has given approval to the final form of this revision.

Thank you for your considerations.

Sincerely.

Dr. Bilal LITIM

Corresponding author

List of responses:

- **Answers For Editor:** thank you for insightful comments.

  We have checked carefully the guide for authors, and we have made the necessary correction in the revised manuscript.

- **Answers For reviewer 3:** thank you for insightful comments.

  **I-** In the introduction section:
1- We have deleted the sentence with its reference “The rapid emergence of multidrug-resistant (MDR) bacteria has been related to a waning antibiotic development (1)”, to avoiding the repetition with the other sentences, and give more clarity for the introduction section.

2- The sentence “The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) categorize antimicrobial-resistant (AMR) pathogens as an alarming health threat worldwide..” correct to “…According to the World Health Organization (WHO), bacterial infections are among the top ten causes of morbidity and mortality worldwide”.

3- The sentence “Currently, many reports estimate that more …..” correct to “Data from the World Health Organization has revealed that …”.

4- The sentence “Based on these facts, the discovery of novel and potent antibacterial drugs is a vital step to overcome bacterial resistance and develop effective therapies” correct to “Based on these facts, the discovery of new and effective drugs must be discovered to overcome bacterial resistance and develop effective treatments..”

5- The sentences “Naturally, quinolines and their derivatives are well-known as clinically useful drugs for treating microbial infection diseases and present different antimicrobial mechanisms (7). Recent studies have drawn attention to the use of quinoline moiety as potent antimicrobial agents (8,9), these great attentions paid by medicinal researchers explained by their broad spectrum of biological activities “ correct to “ 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.”.

6- The sentence “and recently, many research reports have supported using of chloroquine and hydroxychloroquine (antimalarial drugs), as inhibitors of SARS-CoV-2 (Covid-19) virus to fight the current pandemic.” correct to “and as inhibitors of SARS-CoV-2 (Covid-19) virus [15–17]. Therefore, compounds containing thiazole heterocycles are well known in medicinal chemistry”.

7- The sentences “In addition, coumarins having various substituted thiazole rings show promising biological activities (25). Coumarin–thiazole compounds have shown potential biological activities” correct to “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”.

8- The sentence “the reaction generally requires various expensive and toxic catalysts (37–42), most of them posed various limitations like highly hard conditions, low yields, long reaction times, high reaction temperature, tedious workup and the use of organic solvents, which cause environmental pollution” correct to “the reaction generally requires various catalysts, such as CF$_3$CO$_2$H [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]”. We have thought that if we put examples for the toxic catalysts they will serve to clear the meaning of the other sentence.
The paragraph “Combining multiple pharmacophores within the same structure is an important means to synthesize new bioactive molecules, and it is considered also the main way to create new compounds with moderate biological activities. Based on the above facts, and keeping in view the wide range of pharmaceutical activities of quinoline/quinolone, thiazole substituted, and α-aminophosphonates scaffolds, we have thought that the combination of these moieties in the same scaffold might improve the biological activity against microbial strains, in this work, we have designed and synthesized a series of novel α-aminophosphonates bearing quinoline/quinolone, and thiazole substituted coumarin or phenyl ring using Kabachnik–Fields reaction under ultrasonic irradiation and solvent-free conditions, and evaluated for their antibacterial and antifungal activities.” Correct to “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.”

II- In the results and discussions section:

Chemistry section:

1- The sentence “Our design strategy is that the synthesis of new α-aminophosphonates was modified and containing new pharmacophore (quinoline/quinolone) to improve and discover newly bioactive molecules.”
Correct to “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.

2- The sentence “In the first stage, we started our study with the synthesis of aldehyde derivatives” correct to “The first step of the synthesis involved formation of aldehyde derivatives”.

3- The sentence “quinoline and quinolone derivatives..” correct to “quinoline/quinolone carbaldehyde…”.

4- The sentence “with Vilsmeier–Haack reagent” correct to “which included the condensation of acetanilide derivatives with Vilsmeier–Haack reagent. To improve the meaning of the previous sentence.

5- The sentence “Compounds (8a–b) were synthesized with a simple reaction between 2-Chloro-quinoline-3-carbaldehyde derivatives and Clorohydric acid (HCl 37%) for an appropriate time” correct to “As a continuation, compounds (8a–b) were obtained when treating 2-Chloro-quinoline-3-carbaldehyde derivatives in the presence of Clorohydric acid (HCl 37%)”.

6- The paragraph “using the ionic liquid under ultrasound irradiation. We have found that the ionic liquid [TEAA] had a high advantage for the synthesis of α-aminophosphonate derivatives and showed many remarkable effects in yield and time reaction with a simple work-up. These proprieties offer a wide path in our study. This important technique is widely used today in organic synthesis and offers many advantages such as giving pure product without chromatography purification and excellent yield in short reaction time, low cost, and an environmental synthesis “green chemistry” correct to “using the ionic liquid [TEAA] under ultrasound 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 work-up”.

**In the antimicrobial activity section:**

- We have added the paragraph “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”, to give more clarity and explanation of the results.

- The sentence “The results clearly showed that…” correct to “The results listed in table 4 are clearly showed that…”, because we have put the antifungal results in a separate table (table 4).

Thank you for your consideration of this manuscript.