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RESEARCH ARTICLE

Preparation, spectroscopic, and biological characterizations of novel α-aminophosphonates bearing paracetamol

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ABSTRACT

Background: α-Aminophosphonate derivatives have an important biological activity against bacteria, fungi, and anticancer activity. **Aims and Objectives**: This study aims to study preparation, spectroscopic, and biological characterizations of novel α-aminophosphonates bearing paracetamol. **Materials and Methods:** A series of α-aminophosphonate analogs and arylidene derivatives were synthesized, monitored by thin-layer chromatography, purified by chromatographic methods, and the structures were elucidated by spectroscopic methods such as H nuclear magnetic resonance. The synthesized compounds were tested for their antibacterial activity by hole well method against *Escherichia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive), the antibacterial activity was evaluated based on inhibition zone size around dishes against Gram-positive. **Results**: Compounds 7e, 8a, 7c, 8b, and 8g are showed different degree of inhibitory effect against *S. aureus*; on the other hand in Gram-negative, the compounds 7a, 7c, 7d, 7e, 8a, 8b, and 8g are showed different degree of inhibitory effect against *E. coli*. In this study, we concluded that the results showed that increasing the zone inhibition in compared with amoxicillin and tetracycline against *E. coli* and *S. aureus*. Most of the compounds tested against microbes showed a moderate to high effect while few compounds showed a low antimicrobial effect. **Conclusion**: In this study, we recommended that α-aminophosphonate and arylidene derivatives used as antimicrobial agents.

KEY WORDS: Arylidene Derivatives; α-Aminophosphonates; Antimicrobial activity

INTRODUCTION

Acetaminophen is used in widely range as an analgesic[1] and antipyretic.[2] Paracetamol is classified as a member of the nonsteroidal anti-inflammatory drug. Acetaminophen and different acetaminophen derivatives are very important products which have been found to maintain important pharmacological activity are represent significant moiety in synthesis of new medical compounds, ferocity of pharmacological activities have been assigned to them such as anti-inflammatory,[3-5] antioxidant,[6] and analgesic.[5-7] The main structure of acetaminophen exhibits few or no anti-inflammatory effect in animals[8,9] and alignment anti-inflammatory activity in human.[10] α-Aminophosphonates and their derivatives are important products owning various and beneficial biological activities.[11] α-Aminophosphonates are comparable to amino acids and have found implementations ranging from agriculture to medicine, for

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example, antibiotics,[12] anticancer agents,[13] and enzyme inhibitors.[14] These biological activities are especially related to the tetrahedral structure of the phosphonyl group.[15] The access of using patents, into the cell two conformable or diverse phosphorus-linked antiviral nucleosides, has received great attention.[16-24] A one-step synthesis of phosphonates is offered starting from convenient β-ketophosphonates. The opener step in the preparation includes a one-pot addition and heteroannulation series.[25] The effective stereoselective preparation of the opener intermediate (SS, R)-6 permits simple incoming into a chain of differently substituted α-aminophosphonates through the Suzuki coupling reaction.[26] Dialkylheteroaryl phosphonates were showed in higher yields by one pot but through Michaelis-Arbuzov rearrangement in two-component reaction between heteroaryl halides and trialkyl phosphites in the presence of CeCl3.7H2O as a catalyst in THF at 50–55°C. CeCl3.7H2O was acted as Lewis acid catalyst; the advantages are shorter reaction times, low cost of the starting chemicals, and simple experimental procedure. All the title compounds exhibited promising antibacterial and antifungal activities.[27]

MATERIALS AND METHODS

Chemistry

Melting points were determined with a Kofler block apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Perkin-Elmer model 1720 Fourier transform-IR spectrometer for KBr discs. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 NMR spectrometer at 300 MHz for ^{1}H NMR with tetramethylsilane as a standard. The progress of the reactions was monitored by thin-layer chromatography (TLC) using aluminum silica gel plates 60 F 245. Elemental analyses were performed at the microanalytical data center at Faculty of science, Cairo University, Egypt.

N-(4-(2-Hydrazinyl-2-oxoethoxy)phenyl)acetamide (1)[28]

A mixture of ester (2.37 g, 0.1 mole), hydrazine hydrate (1.5 g, 0.3 mole), and ethanol (30 ml) was heated under reflux for 5 h (TLC). The product was filtered off, recrystallized from ethanol to yield white needles in 90% yield. White needles (90%), m.p. 145–147°C R_f= 0.31 (5% MeOH in $CHCl_3$). ^{1}H NMR (DMSOdR6R): δ = 1.99 (s, 3H, CH_3), 4.31 (brs, 2H, NH_2), 4.42 (s, 2H, CH_2), 6.89 (d, 2H, J= 5.5 Hz, Ar-H), 7.47 (d, 2H, J= 5.5 Hz, ArH), 9.30 (brs, 1H, NH), 9.79 (brs, 1H, NH).

N-(4-(2-(2-(4-Hydroxybenzylidene)hydrazinyl)-2-oxoethoxy)phenyl)acetamide (3)

A mixture of acid hydrazide 1 (2.23 g, 0.01 mole), p-hydroxybenzaldehyde (2) (1.06 g, 0.01 mole), and ethanol (30 ml) in the presence of acetic acid as catalyst was heated under reflux for 6 h (TLC). The solvent was evaporated and the formed precipitate was filtered off, recrystallized from ethanol to yield white powder in 93% yield, m.p. 202–204°C Rf = 0.31 (5% MeOH in $CHCl_3$). 1H NMR (DMSO-d6): δ = 1.98 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 5.50 (s, 1H, OH), 6.75–7.76 (m, 8H, Ar-H), 8.32 (s, 1H, CH), 9.45 (brs, 1H, NH), 9.82 (brs, 1H, NH). Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.54; H, 5.21; N, 12.81.

N-(4-(2-(2-(4-(2-Hydrazinyl-2-oxoethoxy)benzylidene) hydrazinyl)-2-oxoethoxy)phenyl)-acetamide (4)

A mixture of Schiff base derivative 3 (3.27 g, 0.01 mole), ethyl chloroacetate (1.225 g, 0.01 mole), and potassium carbonate (1.38 g, 0.01 mole) in dry acetone (50 ml) was heated under reflux for 8 h (TLC). The solvent was evaporated and the formed precipitate was filtered off, recrystallized from ethanol to yield white crystals in 95% yield, m.p.182–184°C R_f = 0.31 (5% MeOH in $CHCl_3$). IR (KBr) (ν, cm^{-1}): 3336 (NH), 1735 (C=O), 1455 (CH_2), 1375 (CH_3); ^{1}H NMR (DMSO-d_6): δ = 1.30 (t, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.20 (q, 2H, CH_2), 4.82 (s, 4H, $2CH_2$), 6.92–7.87 (m, 8H, Ar-H), 8.38 (s, 1H, CH), 9.50 (brs, 1H, NH), 9.92 (brs, 1H, NH); MS m/z (%) 413. Anal. calculated for $C_{21}H_{23}N_3O_6$: C, 61.01; H, 5.61; N, 10.16. Found: C, 61.11; H, 5.64; N, 10.23.

N-(4-(2-(2-(4-(2-Hydrazinyl-2-oxoethoxy)benzylidene) hydrazinyl)-2-oxoethoxy)-phenyl)acetamide (5)

A mixture of ester derivative 4 (4.13 g, 0.01 mole) and hydrazine hydrate (1.5, 0.03 mole) in absolute ethanol (30) ml was heated under reflux for 12 h (TLC). The solvent was evaporated and the formed precipitate was filtered off, recrystallized from ethanol to yield white powder in 88% yield, m.p. 164–166°C R_f = 0.31 (5% MeOH in $CHCl_3$). IR (KBr) (ν, cm^{-1}): 3336 (NH), 1670 (C=O); ^{1}H NMR (DMSO-d_6): δ = 2.04 (s, 3H, CH_3), 4.50 (brs, 2H, NH_2), 4.72 (s, 4H, $2CH_2$), 6.74–7.85 (m, 8H, Ar-H), 8.34 (s, 1H, CH), 9.42 (brs, 1H, NH), 9.75 (brs, 1H, NH), 9.96 (brs, 1H, NH); MS m/z (%) 400 (M^++1). Anal. calculated for $C_{19}H_{21}N_5O_5$: C, 57.14; H, 5.30; N, 17.53. Found: C, 57.35; H, 5.28; N, 17.62.

N-(4-(2-(2-(4-(2-(2-Formylhydrazinyl)-2-oxoethoxy) benzylidene)hydrazinyl)-2-oxoethoxy)-phenyl) acetamide (6)

A mixture of hydrazide derivative 5 (3.99 g, 0.01 mole) in formic acid (20) ml was heated under reflux for 24 h (TLC). The solvent was evaporated and the formed precipitate was filtered off, recrystallized from ethanol to yield yellow powder in 74% yield, m.p.215–217°C R_f = 0.31 (5% MeOH in $CHCl_3$). ^{1}H NMR (DMSO-d_6): δ = 2.05 (s, 3H, CH_3), 4.62 (s, 4H, $2CH_2$), 6.76–7.88 (m, 8H, Ar-H), 8.32 (s, 1H, CH), 9.45 (brs, 1H, NH), 9.75 (brs, 1H, NH), 9.96 (brs, 1H, NH), 10.22 (s, 1H, CHO). Anal. calculated for $C_{20}H_{21}N_5O_6$: C, 56.20; H, 4.95; N, 16.39. Found: C, 56.06; H, 5.02; N, 16.47.

General Procedure for Preparation of Phosphonate 7 (a-e)

A mixture of the Schiff base 6 (0.01 mole), triphenyl phosphite (0.01 mole), and different amines (0.01 mole) was dissolved in acetonitrile and then perchloric acid (1 ml) was added dropwise, and the reaction was stirred at room temperature overnight (TLC). The solvent was evaporated under reduced pressure, and the residue was titrated with diethyl ether and dried to give 7 (a-e) in 70–85% yields.

Diphenyl((2-(2-(4-((2-(2-(4-acetamidophenoxy)acetyl) hydrazono)methyl)phenoxy)acetyl)-hydrazinyl) ((2-nitrophenyl)amino)methyl)phosphonate (7a)

Red gum (70%), R_f = 0.75 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.98 (s, 3H, CH_3), 2.05 (brs, 1H, NH), 3.85 (brs, 1H, NH), 4.65 (s, 4H, $2CH_2$), 5.95 (s, 1H, CH), 7.02-8.08 (m, 22H, Ar-H), 8.11 (brs, 2H, 2NH), 8.35 (s, 1H, CH), 9.45 (brs, 1H, NH). Anal. calculated for $C_{38}H_{36}N_7O_{10}P$: C, 58.39; H, 4.64; N, 12.54. Found: C, 58.12; H, 4.50; N, 12.12.

Diphenyl((2-(2-(4-((2-(2-(4-acetamidophenoxy)acetyl) hydrazono)methyl)phenoxy)acetyl)-hydrazinyl) (p-tolylamino)methyl)phosphonate (7b)

Red gum (73%), R_f = 0.75 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 2.05 (brs, 1H, NH), 2.40 (s, 3H, CH_3), 3.83 (brs, 1H, NH), 4.65 (s, 4H, $2CH_2$), 5.95 (s, 1H, CH), 6.52-7.56 (m, 22H, Ar-H), 8.00 (brs, 2H, 2NH), 8.22 (s, 1H, CH), 9.14 (brs, 1H, NH). Anal. calculated for $C_{39}H_{39}N_6O_8P$: C, 62.39; H, 5.24; N, 11.19. Found: C, 62.49; H, 5.29; N, 11.33.

Diphenyl((2-(2-(4-((2-(2-(4-acetamidophenoxy)acetyl) hydrazono)methyl)phenoxy)acetyl)-hydrazinyl) (naphthalen-1-ylamino)methyl)phosphonate (7c)

Yellow powder (80%), m.p. >300°C R_f = 0.75 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 2.05 (brs, 1H, NH), 3.83 (brs, 1H, NH), 4.63 (s, 4H, CH_2), 6.00 (s, 1H, 2CH), 7.11–8.00 (m, 25H, Ar-H), 8.15 (brs, 2H, 2NH), 8.37 (s, 1H, CH), 9.11 (brs, 1H, NH). Anal. calculated for $C_{42}H_{39}N_6O_8P$: C, 64.12; H, 5.00; N, 10.68. Found: C, 64.02; H, 4.95; N, 10.17.

Diphenyl((2-(2-(4-((2-(2-(4-acetamidophenoxy)acetyl) hydrazono)methyl)phenoxy)acetyl)-hydrazinyl) ((4-methoxyphenyl)amino)methyl)phosphonate (7d)

Brown powder (82%), m.p. 285–287°C R_f = 0.75 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 2.05 (brs, 1H, NH), 3.75 (brs, 1H, NH), 3.90 (s, 3H, OCH_3), 4.63 (s, 4H, $2CH_2$), 5.85 (s, 1H, CH), 6.76–7.85 (m, 22H, Ar-H), 8.11 (s, 1H, CH), 8.45 (brs, 2H, 2NH), 9.20 (brs, 1H, NH). Anal. calculated for $C_{39}H_{39}N_6O_9P$: C, 61.09; H, 5.13; N, 10.96. Found: C, 59.75; H, 4.92; N, 10.57.

Diphenyl((2-(2-(4-((2-(2-(4-acetamidophenoxy)acetyl) hydrazono)methyl)phenoxy)acetyl)-hydrazinyl)(pyridin-2-ylamino)methyl)phosphonate (7e)

Brown gum (85%), R_f = 0.75 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.95 (s, 3H, CH_3), 2.05 (brs, 1H, NH), 3.75 (brs, 1H, NH), 4.65 (s, 4H, $2CH_2$), 5.85 (s, 1H, CH), 6.76–7.85 (m, 22H, Ar-H), 8.00 (s, 1H, CH), 8.45 (brs, 2H, 2NH), 9.35 (brs, 1H, NH). Anal. calculated for C37H36N7O8P: Calculated: C, 60.24; H, 4.92; N, 13.29. Found: C, 60.44; H, 5.09; N, 13.42.

Reaction of (5) with Different Aromatic Aldehydes to Afford the Corresponding Arylidines 8 (a-g)

To the solution of 5 (0.01 mole) in absolute ethanol, different aromatic aldehydes (0.01 mole) were added and then glacial acetic acid (1 ml) was added to the reaction mixture which refluxed for 15 h (TLC). The solvent was evaporated or concentrated under reduced pressure, and the product was filtered off to afford 8(a-g) (86–92%) yields.

***N*-(4-(2-((2)-2-(4-(2-(2-(4-Hydroxybenzylidene) hydrazinyl)-2-oxoethoxy)benzylidene)-hydrazinyl)-2-oxoethoxy)phenyl)acetamide (8a)**

Yellow crystals (86%), m.p. 225–227°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 4.60 (s, 4H, $2CH_2$), 5.30 (s, 1H, OH), 6.80–7.55 (m, 12H, Ar-H), 8.05 (brs, 2H, 2NH), 8.38 (s, 2H, 2CH), 9.35 (brs, 1H, NH); MS m/z (%) 505 (M^++2). Anal. calculated for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 61.82; H, 5.08; N, 14.11.

***N*-(4-(2-(-2-(4-(2-(-2-Benzylidenehydrazinyl)-2-oxoethoxy)benzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (8b)**

Yellow crystals (86%), m.p. 240–242°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 2.06 (s, 3H, CH_3), 4.65 (s, 4H, $2CH_2$), 6.75-7.60 (m, 13H, Ar-H), 8.00 (brs, 2H, 2NH), 8.35 (s, 2H, 2CH); MS m/z (%) 487. Anal. calculated for $C_{26}H_{25}N_5O_5$: C, 64.06; H, 5.17; N, 14.37. Found: C, 64.24; H, 5.30; N, 14.55.

***N*-(4-(2-(2-(4-(2-(2-(2-Hydroxybenzylidene)hydrazinyl)-2-oxoethoxy)benzylidene)-hydrazinyl)-2-oxoethoxy) phenyl)acetamide (8c)**

Orange crystals (88%), m.p. 235–237°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 2.00 (s, 3H, CH_3), 4.61 (s, 4H, $2CH_2$), 5.30 (s, 1H, OH), 6.92–7.60 (m, 12H, Ar-H), 8.10 (brs, 2H, 2NH), 8.40 (s, 2H, 2CH), 9.35 (brs, 1H, NH); MS m/z (%) 503. Anal. Calcd for Anal. calculated for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 62.20; H, 5.20; N, 14.05.

***N*-(4-(2-Oxo-2-(2-(4-(2-oxo-2-(2-(3,4,5-trimethoxybenzylidene)hydrazinyl)ethoxy)-benzylidene) hydrazinyl)ethoxy)phenyl)acetamide (8d)**

Yellow powder (90%), m.p. >300°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 1.99 (s, 3H, CH_3), 3.85 (s, 9H, 3OCH_3), 4.63 (s, 4H, 2CH_2), 7.12–7.84 (m, 10H, Ar-H), 8.15 (brs, 2H, 2NH), 8.38 (s, 2H, 2CH), 9.12 (brs, 1H, NH); MS m/z (%) 577. Anal. calculated for $C_{29}H_{31}N_5O_8$: Calculated: C, 60.30; H, 5.41; N, 12.13. Found: C, 60.54; H, 5.35; N, 12.27.

***N*-(4-(2-(2-(4-(2-(2-(4-Nitrobenzylidene)hydrazinyl)-2-oxoethoxy)benzylidene)-hydrazinyl)-2-oxoethoxy) phenyl)acetamide (8e)**

White powder (92%), m.p. 278–280°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 2.10 (s, 3H, CH_3), 4.65 (s, 4H, 2CH_2), 7.22–8.33 (m, 12H, Ar-H), 8.05 (brs, 2H, 2NH), 8.55 (s, 2H, 2CH), 9.31 (brs, 1H, NH); MS m/z (%) 532. Anal. calculated for $C_{26}H_{24}N_6O_7$: Calculated: C, 58.64; H, 4.54; N, 15.78. Found: C, 58.94; H, 5.11; N, 16.04.

***N*-(4-(2-(2-(4-(2-(2-(4-(Dimethylamino)benzylidene) hydrazinyl)-2-oxoethoxy)-benzylidene)hydrazinyl)-2-oxoethoxy)phenyl)acetamide (8f)**

White powder (91%), m.p. >300°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 2.04 (s, 3H, CH_3), 3.10 (s, 6H, 2CH_3), 4.62 (s, 4H, 2CH_2), 6.82-7.51 (m, 12H, Ar-H), 8.00 (brs, 2H, 2NH), 8.35 (s, 2H, 2CH), 9.31 (brs, 1H, NH); MS m/z (%) 530. Anal. calculated for $C_{28}H_{30}N_6O_5$: C, 63.38; H, 5.70; N, 15.84. Found: C, 63.68; H, 5.78; N, 16.02.

***N*-(4-(2-Oxo-2-(2-(4-(2-oxo-2-(2-(pyridin-2-ylmethylene) hydrazinyl)ethoxy)benzylidene)-hydrazinyl)ethoxy) phenyl)acetamide (8g)**

Brown powder (90%), m.p. >300°C R_f = 0.45 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ = 2.04 (s, 3H, CH_3), 4.62 (s, 4H, 2CH_2), 7.12–7.87 (m, 12H, Ar-H), 8.10 (brs, 2H, 2NH), 8.39 (s, 2H, 2CH), 9.51 (brs, 1H, NH); MS m/z (%) 488. Anal. calculated for $C_{25}H_{24}N_6O_5$: C, 61.47; H, 4.95; N, 17.20. Found: C, 61.88; H, 5.13; N, 17.55.

Tested Microorganisms

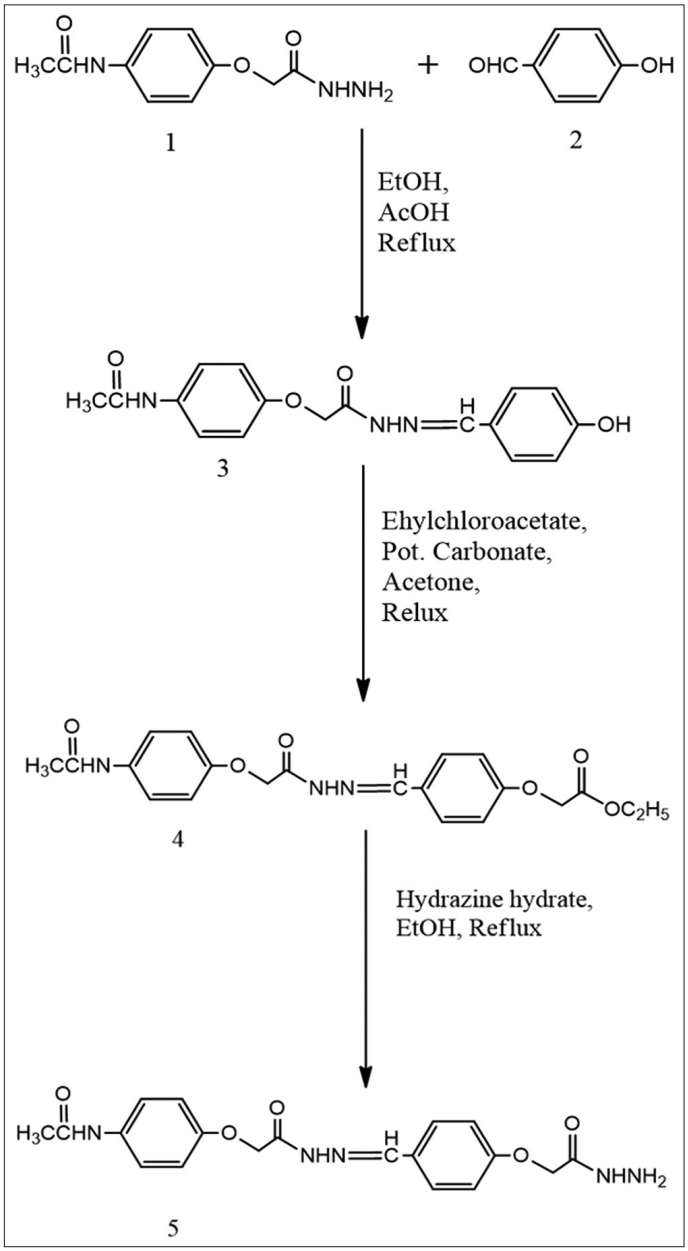
Two bacterial strains, namely *Staphylococcus aureus* and *Escherichia coli* were used in this study. All bacterial cultures were obtained from Faculty of Veterinary Medicine, Sadat City University; the media used for antibacterial sensitivity test were Muller–Hinton Agar.

Antibacterial Sensitivity Test

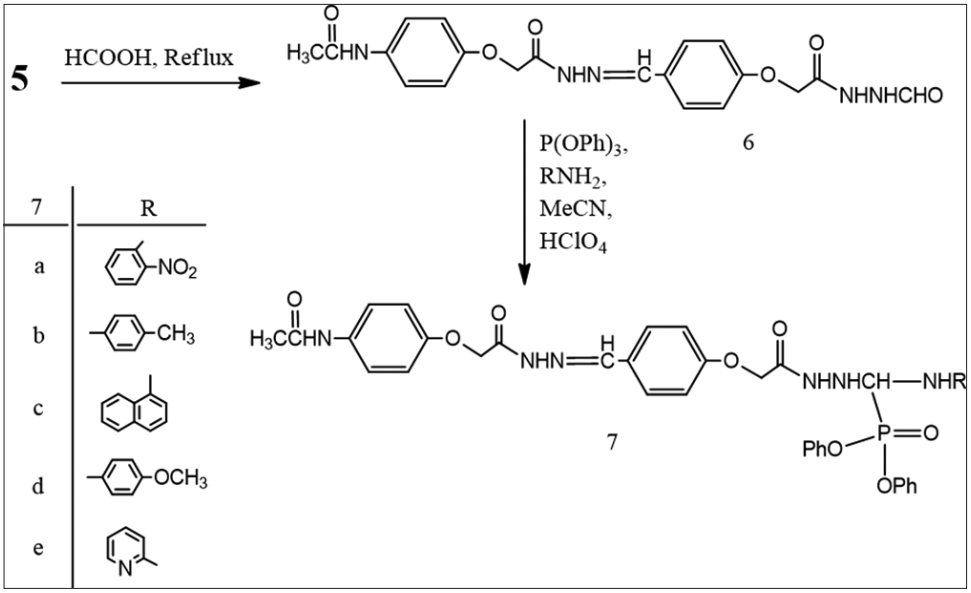
The test was carried out by preparing fresh colonies (24 h cultures) of *S. aureus* and *E. coli*. The intermediary media for the growth of bacteria was sterilized by autoclave at 120°C (15 lb/in2). Approximately 30 ml of the Muller–Hinton agar medium was poured in the sterile plates, then lifted at room temperature for solidification. A well of 6 mm diameter was made using a sterile cork borer. The synthesized compounds were placed in 6 mm diameter well; plates were incubated at 37°C for 24 h and reading of the inhibition zone.[29]

RESULTS

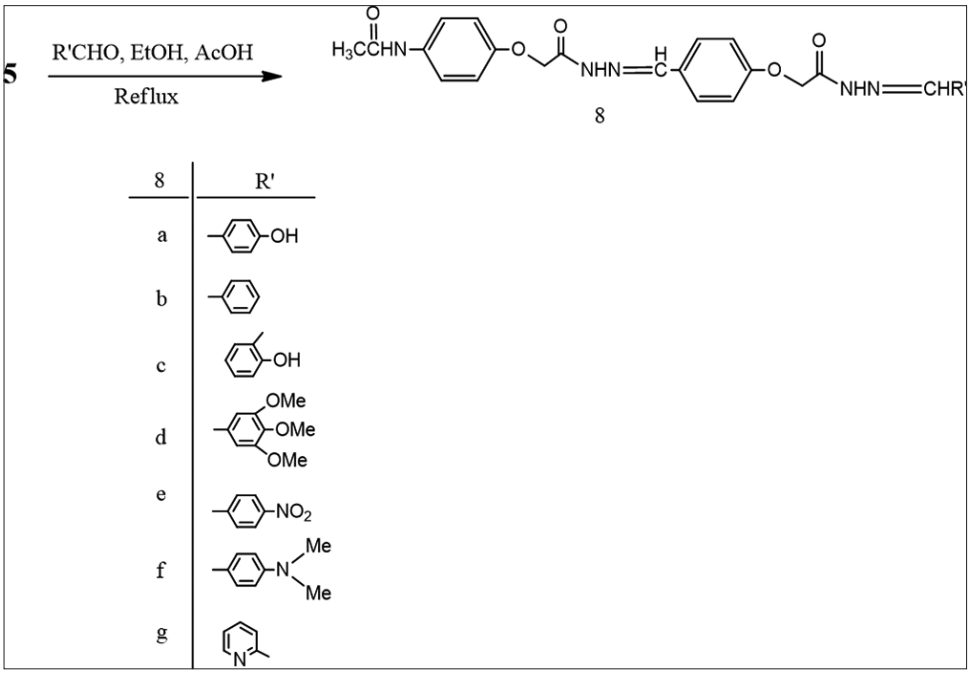
The chemistry and antimicrobial activity of compounds are presented in Schemes 1–3 and Table 1, respectively.



Scheme 1: Reaction of prepared hydrazide with p-hydroxybenzaldehyde in acidic condition



Scheme 2: Reaction of hydrazide 5 with formic acid under reflux



Scheme 3: Reaction of hydrazide with different aldehydes

DISCUSSION

Chemistry

In Scheme 1, the prepared hydrazide is allowed to react with *p*-hydroxybenzaldehyde in acidic condition under reflux to afford the corresponding imine 3. The ^{1}HNMR showed the appearance of the proton of the imine carbon at 9.45 and the phenolic OH at 5.50. The hydrazide 5 is obtained by the reaction of imine 3 with ethyl chloroacetate in acetone and in the presence of potassium carbonate to afford the ester 4 which is reacted with hydrazine hydrate in ethanol to form the product. The IR spectra of ester 4 showed the formation of the carbonyl group at 1735 which is changed to 1670 of the corresponding hydrazide 5. The ^{1}HNMR of the ester 4 showed the appearance of the ethyl group as triplet at 1.30 and quartet at 4.20 for CH_3 and CH_2, respectively.

In Scheme 2, the phosphonates 7a-e are resulted by the reaction of hydrazide 5 with formic acid under reflux to get the corresponding aldehyde 6 which is participated in three-component reaction with triphenyl phosphite and amine in the presence of perchloric acid to afford the products. ^{1}HNMR of the aldehyde 6 showed the proton of CHO at 10.22 which is changed to appear in the range of 5.85–6.00 of the phosphonates 7a-e.

Table 1: Antibacterial activity of different synthesized compounds

Compound	*S. aureus*	Zone of inhibition	*E. coli*	Zone of inhibition
7a	(+)	14 mm	(++)	14 mm
7b	(+)	11 mm	(+)	15 mm
7c	(++)	10 mm	(++)	10 mm
7d	(−)	-----	(+++)	16 mm
7e	(++)	11 mm	(++)	10 mm
8a	(++)	12 mm	(++)	11 mm
8b	(+++)	16 mm	(+++)	16 mm
8c	(−)	-----	(+)	14 mm
8d	(−)	-----	(−)	-----
8e	(+)	12 mm	(+)	13 mm
8f	(+)	16 mm	(−)	-----
8g	(+++)	16 mm	(++)	14 mm

(+): Low, (++): Intermediate, (+++): High, (−): Negative activity, (-----): No inhibition

In Scheme 3, the hydrazide is reacted with different aldehydes to the form of corresponding arylidene derivatives 8a-g. The ^{1}HNMR of hydrazide 5 showed singlet peak of NH_2 at 4.50 which is changed to appear at the range of 8.35–8.39 of *CH* of arylidene derivatives.

Antimicrobial Activity

In Table 1, the antibacterial activity was evaluated based on inhibition zone size around dishes against Gram-positive. Compounds 7e, 8a, 7c, 8b, and 8g are showed different degree of inhibitory effect against *S. aureus*; on the other hand in Gram-negative, the compounds 7a, 7c, 7d, 7e, 8a, 8b, and 8g are showed different degree of inhibitory effect against *E. coli*. The results showed that increasing the zone inhibition in compared with amoxicillin and tetracycline against *E. coli* and *S. aureus*. Most of the compounds tested against microbes showed a moderate to high effect while few compounds showed a low antimicrobial effect.

CONCLUSION

In this research, new α-aminophosphonates bearing paracetamol moiety was synthesized. The antimicrobial activity of new synthesized compounds was tested and showed moderate to high antimicrobial activity against *E. coli* and *S. aureus*.

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