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RESEARCH ARTICLE

Synthesis of some new 1,3,4-oxadiazole derivatives bearing sugars and α-aminophosphonate derived from 4-nitrophenol as anticancer agents

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ABSTRACT

Background: 1,3,4-oxadiazoles square measure a very important category of heterocyclic compounds with a broad variety of biological activities such as medicament, analgesic, ulcerogenicity, apoptosis inducer, anti-mycobacterial, antifungal, antitumor, P-glycoprotein Inhibitors, pesticides, 4-hydroxylase inhibitors, and antiepileptic drug activity. **Aims and Objectives:** The present study is undertaken to study the evaluation of new 1,3,4-oxadiazole derivatives bearing sugars and α-aminophosphonate derived from 4-nitrophenol as anticancer agents. **Materials and Methods:** A sequence of acyclic nucleoside derivatives, arylidines, oxadiazole, and α-aminophosphonates derived from 1,3,4-oxadiazole moiety were synthesized, observed by thin-layer chromatography, and purified by crystallization and another chromatographic methods; then, the prepared compounds were confirmed chemically by spectroscopic analysis such as infrared, mass spectra, and ^{1}H nuclear magnetic resonance and also elucidated by elemental analysis. **Results:** The synthesized compounds were tested for their anticancer activity by measuring the inhibitory activity against hepatocellular carcinoma cell method under conditions with 50% inhibitory concentration (IC_{50}) = 38.8 ± 5.4 μg/ml, IC_{50} = 89.1 ± 7.6 μg/ml, IC_{50} = 25.4 ± 3.8 μg/ml, IC_{50} = 90.2. ± 8.1 μg/ml, IC_{50} = 86.9 ± 7.9 μg/ml, IC_{50} = 248 ± 19.6 μg/ml, and IC_{50} = 12.5 ± 4.7 μg/ml for compounds 3, 7a, 9a, 11d, 13b, 15e, and 16a, respectively. 5-fluorouracil was used as reference anticancer drug in this work. **Conclusion:** The synthesized compounds 3 (hydrazide), 7a and 9a (acyclic nucleosides), 11d (arylidines derivative), 13b (oxadiazoline derivative), and 15e and 16a (α-aminophosphonate derivatives) show moderate-to-high activity against hepatocellular carcinoma cells.

Key words: α-aminophosphonates; Arylidines Derivatives; Oxadiazole; Anticancer Activity

INTRODUCTION

1,3,4-oxadiazoles square measure a very important category of heterocyclic compounds[1] with a broad variety of biological activities such as medicament, analgesic, ulcerogenicity,[2] apoptosis inducer,[3] antimycobacterial,[4] antifungal,[5] antitumor,[3,6] P-glycoprotein inhibitors,[7] pesticides,[8] 4-hydroxylase inhibitors,[9] and antiepileptic drug activity[10]. The antitumor properties of the synthesized oxadiazole moieties were estimated by measuring their capability of inhibitingneoplastic cell growth in pathology fluid of Swiss unusual person mice.[11] Cancer is one of the greatest challenges facing human beings with difficulty in dealing and standing against it. Cancer is a very important ailment that affects around over 7 million peoples worldwide annually.[12] Potential toxicity impact of the freshly prepared

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compounds, antiestrogen, and a reference medication such as 5-fluorouracil was estimated in four concentrations, by sulforhodamine B assay.[13] Therapy of cancer is related to numerous adverse effects, namely, bone marrow depression, alopecia, and drug evoked cancer and is commonly related to toxicity and genotoxicity to traditional cells along with the event of resistance.[14] Recently, medical chemists have been looking for new drugs to be used safely to treat cancer. The receptor of circular protein (epidermal growth factor receptor) plays an essential role in cancer proliferation and it is suggested that any agent would inhibit the thymidine kinase activity should have a potential role in tumor control. Heterocyclic compounds containing nitrogen atom such as oxadiazole moieties are of interest to researchers in the fields of medical and pharmaceutical chemistry.[15]

MATERIALS AND METHODS

General

Melting points of the prepared compounds were determined with apparatus of a Kof. block. The infrared (IR) spectrum was recorded on a model of Perkin Elmer 1720 Fourier-transform infrared spectrometer for KBr discs. Proton nuclear magnetic resonance spectrum of Varian Gemini 200 ^{1}H nuclear magnetic resonance (NMR) Spectrometer at 300 MHz for proton nuclear magnetic resonance was recorded with tetramethylsilane as a standard. Thin-layer chromatography was used to monitor the progress of the reactions using plates of aluminum silica gel 60 F 245. The synthesized compounds were confirmed also by elemental analysis at Faculty of Science, Cairo University, Egypt.

Chemistry

Ethyl 2-(4-nitrophenoxy)acetate (2)

A mixture of p-aminophenol 1 (13.9 g, 100 mmole), anhydrous K_2CO_3 (13.8 g, 100 mmole), ethyl chloroacetate (12.25 g, 100 mmole), and dry acetone (300 ml) was heated for 10 h (thin-layer chromatography [TLC]) under reflux. Then, the result solvent after filtration was evaporated under reduces pressure. The result precipitate was recrystallized from absolute ethanol to give yellow crystals in 95% yield, m.p. 220–222°C R_f = 0.55 (4% methanol in methylene chloride). ^{1}H NMR (dimethyl sulfoxide [DMSO]-d_6): δ = 1.24 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 4.15 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 4.92 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 5.5Hz, H-2), 8.20 (d, 2H, J = 5.5 Hz, H-3); MS m/z (%) 225 (M^+). Anal. Calcd for $C_{10}H_{11}NO_5$: Calcd: C, 53.33; H, 4.92; N, 6.22. Found: C, 53.54; H, 5.02; N, 6.47.

2-(4-nitrophenoxy)acetohydrazide (3)

A mixture of 2 (2.25 g, 10 mmole), ethanol (50 ml), and hydrazine hydrate (1.5 g, 30 mmole) was heated for 5 h (TLC) under reflux. The result compound was filtered off, recrystallized from absolute ethanol to afford white powder in 90% yield, m.p. 190–192°C R_f = 0.40 (4% methanol in methylene chloride). IR spectra (KBr) (^{V}, cm^{-1}): 3336 (NH), 3450 (NH_2), 1645 (C=O); ^{1}HNMR (DMSO-d_6): δ = 2.75 (brs, 2H, NH_2), 4.53 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.20 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.33 (brs, 1H, NH); MS m/z (%) 212 $(M+H)^+$. Anal. Calcd for $C_8H_9N_3O_4$: Calcd: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.74; H, 4.62; N, 18.05.

5-((4-nitrophenoxy)methyl)-1,3,4-oxadiazole-2-thiol (4)

A mixture of hydrazide 3 (2.11 g, 10 mmole), KOH (0.56 g, 10 mmole), carbon disulfide (0.76 g, 0.01 mole), and ethanol (30 ml) was heated for 10 h (TLC) under reflux. The result solvent after filtration was evaporated under reduced pressure, and the result precipitate was dissolved in distilled water and then hydrochloric acid was added to give white precipitate which recrystallized from absolute ethanol to give white powder in 85% yield m.p. 266–268°C R_f = 0.55 (4% methanol in methylene chloride). ^{1}H NMR (DMSO-d_6): d = 4.75 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.10 (d, 2H, *J* = 5.5 Hz, Ar-H), 13.15 (s, 1H, SH); MS m/z (%) 241 $(M+2H)^+$. Anal. Calcd for $C_9H_7N_3O_4S$: Calcd: C, 42.69; H, 2.79; N, 16.59. Found: C, 42.54; H, 2.52; N, 16.75.

Ethyl 2-(5-(4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)thio)acetate (5)

A mixture of 3 (2.39 g, 10 mmole), anhydrous K_2CO_3 (1.38 g, 10 mmole), ethyl chloroacetate (1.225 g, 10 mmole), and dry acetone (30 ml) was heated for 8 h (TLC) under reflux. The result solvent after filtration was evaporated under reduced pressure to give white crystals in 88% yield, m.p. 270–272°C R_f = 0.40 (4% methanol in methylene chloride). ^{1}H NMR (DMSO-d_6): d = 1.27 (t, 3H, *J* = 7.2 Hz, CH_3CH_2), 4.20 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 4.63 (s, 2H, CH_2), 5.14 (s, 2H, CH_2), 7.27 (d, 2H, *J* = 5.5Hz, H-2), 8.15 (d, 2H, *J* = 5.5 Hz, H-3); MS m/z (%) 339 (M^+). Anal. Calcd for $C_{13}H_{13}N3O_6S$: Calcd: C, 46.01; H, 3.86; N, 12.38. Found: C, 46.14; H, 4.02; N, 12.25.

2-(5-(4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)thio) acetohydrazide (6)

A mixture of 6 (3.39 g, 10 mmole), ethanol (30 ml), and hydrazine hydrate (1.5 g, 30 mole) was heated for 7 h (TLC) under reflux. The result precipitate was filtered off and recrystallized from methanol to give white powder in 93% yield, m.p. 176–178°C R_f = 0.40 (4% methanol in methylene chloride). IR (KBr) (^{V}, cm^{-1}): 3336 (NH), 3450 (NH_2), 1645 (C=O), 1450 (CH_2); ^{1}HNMR (DMSO-d_6): δ = 3.53 (brs, 2H, NH_2), 4.24 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.20 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.15 (brs, 1H, NH); MS m/z (%) 325 (M^+). Anal. Calcd for $C_{11}H_{11}N_5O_5S$: Calcd: C, 40.61; H, 3.41; N, 21.53. Found: C, 40.84; H, 3.52; N, 21.35.

General Procedure for the Preparation of Sugar (4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetylhydrazones 7a-d

Acetohydrazide 6 (3.25 g, 10 mmole) in ethanol (35 ml) was added to a solution of monosaccharides (arabinose, glucose, mannose, and galactose), respectively (0.01 mole), and in the presence of AcOH as catalyst. The mixture was heated for 6–9 h (TLC) under reflux, then the excess of ethanol was evaporated, and the solid produced was collected as white powder and recrystallized from ethanol to give sugar hydrazones 7a-d.

L-(-)-Arabinose(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thio acetylhydrazone (7a)

White powder (73%), m.p. 210–213°C. Rf = 0.72 (5% MeOH in CH_2Cl_2), IR spectra (KBr), ν, cm^{-1}: 3340 (OH), 3450 (NH). ^{1}H NMR (300 MHz, DMSO-d6), δ = 3.19–3.65 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-5″), 3.81 (brs, 2H, 2xOH), 3.95 (brs, 2H, 2xOH), 4.10 (s, 2H, CH2), 5.12 (s, 2H, CH_2), 7.35 (d, 1H, *J* = 5.5 Hz, H-1′), 7.45–8.20 (m, 4H, Ar-H), 8.82 (brs, 1H, NH); MS m/z (%) 459 $(M+2H)^+$. Anal. Calcd for $C_{16}H_{19}N_5O_9S$: Calcd: C, 42.01; H, 4.19; N, 15.31. Found: C, 42.14; H, 4.25; N, 15.45.

D-(+)-Glucose(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thio acetylhydrazone (7b)

White powder (75%), m.p. 240–242°C. R_f = 0.72 (5% methanol in methylene chloride), IR spectra spectrum (KBr), ν, cm^{-1}: 3340 (OH), 3450 (NH). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.76 (brs, 1H, OH), 3.35–3.55 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-6″), 3.28 (m, 1H, *J* = 5.5 Hz, H-2’), 3.81 (brs, 2H, 2xOH), 3.98 (s, 2H, CH2), 4.05 (brs, 2H, 2xOH), 5.22 (s, 2H, CH_2), 7.30 (d, 1H, *J* = 5.5 Hz, H-1′), 7.35–8.15 (m, 4H, Ar-H), 8.75 (brs, 1H, NH); MS m/z (%) 487 (M^+). Anal. Calcd for $C_{17}H_{21}N_5O_{10}S$: Calcd: C, 41.89; H, 4.34; N, 14.37. Found: C, 42.00; H, 4.41; N, 14.50.

D-(+)-Mannose(4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)thio) acetylhydrazone (7c)

White powder (70%), m.p. 192–194°C. R_f = 0.72 (5% MeOH in CH_2Cl_2), IR spectra (KBr), ν, cm^{-1}: 3340 (OH), 3450 (NH). ^{1}HNMR (300 MHz, DMSO-d6), δ = 2.85 (brs, 1H, OH), 3.25–3.50 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-6″), 3.30 (m, 1H, *J* = 5.5 Hz, H-2’), 3.75 (brs, 2H, 2xOH), 3.95 (s, 2H, CH2), 4.10 (brs, 2H, 2xOH), 5.35 (s, 2H, CH_2), 7.25 (d, 1H, *J* = 5.5 Hz, H-1′), 7.35–8.15 (m, 4H, Ar-H), 8.80 (brs, 1H, NH); MS m/z (%) 498 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{21}N_5O_{10}S$: Calcd: C, 41.89; H, 4.34; N, 14.37. Found: C, 42.10; H, 4.45; N, 14.45.

D-(+)-Galactose(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thio acetylhydrazone (7d)

White powder (80%), m.p. >300°C. R_f = 0.70 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3340 (OH), 3450 (NH). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.90 (brs, 1H, OH), 3.20–3.48 (m, 5H, H-3′, H-4′, H-5′, H-6′, H-6″), 3.25 (m, 1H, J=5.5 Hz, H-2’), 3.80 (brs, 2H, 2xOH), 3.90 (s, 2H, CH2), 4.20 (brs, 2H, 2xOH), 5.15 (s, 2H, CH_2), 7.25 (d, 1H, J=5.5 Hz, H-1′), 7.30–8.10 (m, 4H, Ar-H), 9.00 (brs, 1H, NH); Anal. Calcd for $C_{17}H_{21}N_5O_{10}S$: Calcd: C, 41.89; H, 4.34; N, 14.37. Found: C, 41.70; H, 4.50; N, 14.27.

General Procedure for the Synthesis of Sugar of Tetra-*O*-acetyl- and Penta-*O*-acetyl (4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thioacetylhydrazones 8a-d

A solution of synthesized sugar hydrazones 7a-d (10 mmole) in pyridine (10 ml) was allowed to react with acetic anhydride (0.06 mole) at room temperature with stirring for overnight. The mixture was poured onto crushed ice. The resultant product was separated as brown powder to give acetylated sugar hydrazones 8a-d.

2,3,4,5-Tetra-O-acetyl-L-(-)-arabinose(4-nitrophenoxy) methyl-1,3,4-oxadiazol-2-yl)thioacetylhydrazones (8a)

Brown powder (65%), m.p. 250–253°C. R_f = 0.70 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1735 (CO). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.10, 2.15, 2.21, 2.24 (4s, 12H, 4xCH_3CO), 4.10 (s, 2H, CH_2), 4.25,4.55 (2m, 2H, H-5′, H-5″), 5.16 (m, 1H, H-4′), 5.05 (m, 1H, H-3′), 4.56 (m, 1H, H-2′), 5.35 (s, 2H, CH_2), 7.50 (d, 1H, *J* = 5.5 Hz, H-1′), 7.40-8.20 (m,4H, Ar-H), 9.10 (brs,1H,NH); MS m/z (%) 625 (M^+). Anal. Calcd for $C_{24}H_{27}N_5O_{13}S$: Calcd: C, 46.08; H, 4.35; N, 11.20. Found: C, 46.10; H, 4.30; N, 11.35.

2,3,4,5,6-Penta-O-acetyl-D-(+)-glucose(4-nitrophenoxy) methyl-1,3,4-oxadiazol-2-yl)thioacetylhydrazones (8b)

Pale-brown powder (70%), m.p. >300°C. R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1735 (CO). ^{1}HNMR (300 MHz, DMSO-d6), δ = 1.99, 2.04, 2.09, 2.10, 2.21 (5s, 15H, 5xCH_3CO), 4.10 (s, 2H, CH_2), 4.22,4.48 (2m, 2H, H-6′,H-6″), 4.56 (m, 1H, H-5′), 5.05 (m, 1H, H-4′), 5.11 (m, 1H, H-3′), 5.14 (m, 1H, H-2′), 5.38 (s, 2H, CH2), 7.54 (d, 1H, *J* = 2.5 Hz, H-1′), 7.27–8.16 (m, 4H, Ar-H), 9.15 (brs, 1H, NH). Anal. Calcd for $C_{27}H_{31}N_5O_{15}S$: Calcd: C, 46.48; H, 4.48; N, 10.04. Found: C, 46.35; H, 4.36; N, 10.20.

2,3,4,5,6-Penta-O-acetyl-D-(+)-mannose (4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetylhydrazones (8c)

White powder (72%), m.p. 270–273°C. R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1735 (CO). ^{1}HNMR (300 MHz, DMSO-d6), δ = 2.00, 2.05, 2.08, 2.12, 2.20 (5s, 15H, 5xCH_3CO), 4.10 (s, 2H, CH_2), 4.20,4.46 (2m, 2H, H-6′,H-6″), 4.58 (m, 1H, H-5′), 5.07 (m, 1H, H-4′), 5.14 (m, 1H, H-3′), 5.20 (m, 1H,

H-2′), 5.35 (s, 2H, CH2), 7.50 (d, 1H, J=2.5 Hz, H-1′), 7.26–8.12 (m, 4H, Ar-H), 9.20 (brs, 1H, NH). Anal. Calcd for $C_{27}H_{31}N_5O_{15}S$: Calcd: C, 46.48; H, 4.48; N, 10.04. Found: C, 46.55; H, 4.60; N, 10.10.

2,3,4,5,6-Penta-O-acetyl-D-(+)-galactose (4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetylhydrazones (8d)

White powder (72%), m.p. 238–240°C. R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1735 (CO). ^{1}HNMR (300 MHz, DMSO-d6), δ = 2.02, 2.07, 2.09, 2.14, 2.23 (5s, 15H, 5xCH_3CO), 4.12 (s, 2H, CH_2), 4.22,4.49 (2m, 2H, H-6′,H-6″), 4.52 (m, 1H, H-5′), 5.10 (m, 1H, H-4′), 5.15 (m, 1H, H-3′), 5.22 (m, 1H, H-2′), 5.35 (s, 2H, CH2), 7.52 (d, 1H, J=2.5 Hz, H-1′), 7.25–8.10 (m, 4H, Ar-H), 9.25 (brs, 1H, NH). Anal. Calcd for $C_{27}H_{31}N_5O_{15}S$: Calcd: C, 46.48; H, 4.48; N, 10.04. Found: C, 46.60; H, 4.31; N, 9.95.

General Procedure for the Synthesis of 4-acetyl-5-(tetra- and penta-*O*-acetylalditolyl)-2-(4-nitrophenoxy)methyl-1,3,4-oxadiazolines 9a-d

A solution of synthesized sugar hydrazones 7a-d (10 mmole) in acetic anhydride (8 ml) was heated at 100°C for 7 h. The mixture was poured onto crushed ice. The precipitate that separated out was filtered off, washed by water, and dried. The products were recrystallized from absolute ethanol to afford oxadiazoline derivatives 9a-d.

4-Acetyl-5-(1,2,3,4-tetra-O-acetyl-L-arabinotetritolyl)-2-(4-nitrophenoxy)methyl-1,3,4-oxadiazoline (9a)

Red gum (60%). R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1740 ($COCH_3$). 1645 (C=N). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.01, 2.06, 2.08, 2.12, 2.19 (5s, 15H, 5xCH_3CO), 3.50 (s, 2H, CH_2), 4.20, 4.50 (2m, 2H, H-4′,H-4″), 5.12 (m, 1H, H-3′), 5.14 (m, 1H, H-2′), 5.40 (s, 2H, CH_2), 5.85 (dd, 1H, *J* = 5.5, 6.2 Hz, H-1′), 5.85 (d, 1H, *J* = 7.2 Hz, oxadiazoline H-5), 7.23–8.11 (m, 4H, Ar-H); MS m/z (%) 706 $(M+K)^+$. Anal. Calcd for $C_{26}H_{29}N_5O_{14}S$: Calcd: C, 46.78; H, 4.38; N, 10.49. Found: C, 46.58; H, 4.35; N, 10.55.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)-2-(4-nitrophenoxy)methyl-1,3,4-oxadiazoline (9b)

Yellow gum (65%). R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1740 ($COCH_3$). 1645 (C=N). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.02, 2.04, 2.06, 2.14, 2.18, 2.24 (6s, 18H, 6xCH_3CO), 3.45 (s, 2H, CH_2), 4.22, 4.48 (2m, 2H, H-5′,H-5″), 5.14 (m, 1H, H-4′), 5.16 (m, 1H, H-3′), 5.18 (m, 1H, H-2’), 5.38 (s, 2H, CH_2), 5.27 (dd, 1H, *J* = 5.5, 6.2 Hz, H-1′), 5.95 (d, 1H, *J* = 7.2 Hz, oxadiazoline H-5), 7.25–8.15 (m, 4H, Ar-H); MS m/z (%) 740 $(M+H)^+$. Anal. Calcd for $C_{29}H_{33}N_5O_{16}S$: Calcd: C, 47.09; H, 4.50; N, 9.47. Found: C, 47.11; H, 4.55; N, 9.60.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-mannopentitolyl)-2-(4-nitrophenoxy)methyl-1,3,4-oxadiazoline (9c)

Yellow gum (55%). R_f = 0.45 (4% methanol in methylene chloride), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1740 ($COCH_3$). 1650 (C=N). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.00, 2.05, 2.08, 2.12, 2.16, 2.21 (6s, 18H, 6xCH_3CO), 3.35 (s, 2H, CH_2), 4.18, 4.45 (2m, 2H, H-5′,H-5″), 5.12 (m, 1H, H-4′), 5.14 (m, 1H, H-3′), 5.21 (m, 1H, H-2’), 5.35 (s, 2H, CH_2), 5.41 (dd, 1H, *J* = 5.5, 6.2 Hz, H-1′), 5.90 (d, 1H, *J* = 7.2 Hz, oxadiazoline H-5), 7.25–8.15 (m, 4H, Ar-H). Anal. Calcd for $C_{29}H_{33}N_5O_{16}S$: Calcd: C, 47.09; H, 4.50; N, 9.47. Found: C, 47.14; H, 4.57; N, 9.58.

4-Acetyl-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)-2-(4-nitrophenoxy)methyl)-1,3,4-oxadiazoline (9d)

Yellow gum (50%). R_f = 0.45 (5% MeOH in CH_2Cl_2), IR spectra (KBr), ν, cm^{-1}: 3450 (NH), 1740 ($COCH_3$). 1640 (C=N). ^{1}H NMR (300 MHz, DMSO-d6), δ = 2.04, 2.07, 2.09, 2.16, 2.18, 2.22 (6s, 18H, 6xCH_3CO), 3.50 (s, 2H, CH_2), 4.25, 4.43 (2m, 2H, H-5′,H-5″), 5.10 (m, 1H, H-4′), 5.12 (m, 1H, H-3′), 5.16 (m, 1H, H-2’), 5.35 (s, 2H, CH_2), 5.40 (dd, 1H, *J* = 5.5, 6.2 Hz, H-1′), 5.85 (d, 1H, *J* = 7.2 Hz, oxadiazoline H-5), 7.20–8.10 (m, 4H, Ar-H). Anal. Calcd for $C_{29}H_{33}N_5O_{16}S$: Calcd: C, 47.09; H, 4.50; N, 9.47. Found: C, 46.98; H, 4.45; N, 9.32.

General Procedures for the Reaction of Hydrazides 3 and 6 with Aromatic Aldehydes to Afford Arylidines Bases 10a-e and 11a-e

To a solution of hydrazides 3 and/or 6 (10 mmole) in ethanol, different aromatic aldehydes (10 mmole) were added, and then, acetic acid (0.5 ml) was added to the reaction mixture which was heated for 6 h (TLC) under reflux. The solvent was evaporated under reduced pressure to afford 10a-e and/or 11a-e, respectively, in 84–92% yields.

N-benzylidene-2-(4-nitrophenoxy)acetohydrazide (10a)

White powder (84%), m.p. 90–92°C. Rf = 0.70 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.60 (s, 2H, CH_2), 7.27–8.20 (m, 9H, Ar-H), 8.40 (s, 1H, CH), 9.10 (brs, 1H, NH); MS m/z (%) 299 (M^+). Anal. Calcd for $C_{15}H_{13}N_3O_4$: Calcd: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.31; H, 4.45; N, 14.10.

N-(2-hydroxybenzylidene)-2-(4-nitrophenoxy) acetohydrazide (10b)

Yellow powder (87%), m.p. 101–103°C. Rf = 0.70 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.65 (s, 2H, CH_2), 5.45 (brs, 1H, OH), 7.10–8.16 (m, 8H, Ar-H), 8.65 (s, 1H, CH), 9.20 (brs, 1H, NH). Anal. Calcd for $C_{15}H_{13}N_3O_5$: Calcd: C, 57.14; H, 4.16; N, 13.33. Found: C, 57.05; H, 4.00; N, 13.43.

N-(4-nitrobenzylidene)-2-(4-nitrophenoxy) acetohydrazide (10c)

Brown powder (86%), m.p. 130–132°C. Rf = 0.70 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.62 (s, 2H, CH_2), 7.20–8.10 (m, 8H, Ar-H), 8.30 (s, 1H, CH), 8.95 (brs, 1H, NH); MS m/z (%) 346 $(M+2H)^+$. Anal. Calcd for $C_{15}H_{12}N_4O_6$: Calcd: C, 52.33; H, 3.51; N, 16.27. Found: C, 52.60; H, 3.76; N, 16.55.

2-(4-nitrophenoxy)-N-(3,4,5-trimethoxybenzylidene) acetohydrazide (10d)

White powder (88%), m.p. 210–213°C. Rf = 0.70 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 3.75 (s, 9H, $3CH_3$), 4.65 (s, 2H, CH_2), 7.05–8.00 (m, 6H, Ar-H), 8.33 (s, 1H, CH), 8.90 (brs, 1H, NH); MS m/z (%) 390 (M^++H). Anal. Calcd for $C_{18}H_{19}N_3O_7$: Calcd: C, 55.53; H, 4.92; N, 10.79. Found: C, 55.46; H, 4.79; N, 10.65.

N-(4-(dimethylamino)benzylidene)-2-(4-nitrophenoxy) acetohydrazide (10e)

White powder (92%), m.p. >300°C. Rf = 0.70 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 3.00 (s, 6H, $2CH_3$), 4.65 (s, 2H, CH_2), 6.85–8.10 (m, 8H, Ar-H), 8.35 (s, 1H, CH), 8.75 (brs, 1H, NH). Anal. Calcd for $C_{17}H_{18}N_4O_4$: Calcd: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.75; H, 5.40; N, 16.45.

N-benzylidene-2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thioacetohydrazide (11a)

Yellow crystal (90%), m.p. 254–256°C. Rf = 0.45 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.05 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 7.25–8.20 (m, 9H, Ar-H), 8.30 (s, 1H, CH), 8.95 (brs, 1H, NH). Anal. Calcd for $C_{18}H_{15}N_5O_5S$: Calcd: C, 52.30; H, 3.66; N, 16.94. Found: C, 52.45; H, 3.75; N, 16.85.

N-(2-hydroxybenzylidene)-2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thioacetohydrazide (11b)

Yellow powder (86%), m.p. 263–265°C. Rf = 0.40 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.00 (s, 2H, CH_2), 5.36 (brs, 1H, OH), 5.45 (s, 2H, CH_2), 7.00–8.10 (m, 8H, Ar-H), 8.80 (s, 1H, CH), 9.45 (brs, 1H, NH). Anal. Calcd for $C_{18}H_{15}N_5O_6S$: Calcd: C, 50.35; H, 3.52; N, 16.31. Found: C, 50.47; H, 3.65; N, 16.45.

N-(4-nitrobenzylidene)-2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thioacetohydrazide (11c)

Yellow gum (88%), R_f = 0.45 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 4.10 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 7.30–8.15 (m, 8H, Ar-H), 8.32 (s, 1H, CH), 8.90 (brs, 1H, NH); MS m/z (%) 458 (M^+). Anal. Calcd for $C_{18}H_{14}N_6O_7S$: Calcd: C, 47.16; H, 3.08; N, 18.33. Found: C, 47.20; H, 3.15; N, 18.43.

N-(3,4,5-trimethoxybenzylidene)-2-(5-(4-nitrophenoxy) methyl-1,3,4-oxadiazol-2-yl)thioacetohydrazide (11d)

Brown gum (85%), R_f = 0.40 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): d = 3.80 (s, 9H, $3CH_3$), 4.00 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 7.12–8.10 (m, 6H, Ar-H), 8.35 (s, 1H, CH), 8.75 (brs, 1H, NH); MS m/z (%) 503 (M^+). Anal. Calcd for $C_{21}H_{21}N_5O_8S$: Calcd: C, 50.10; H, 4.20; N, 13.91. Found: C, 50.20; H, 4.35; N, 14.02.

N-(4-(dimethylamino)benzylidene)-2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetohydrazide (11e)

Red gum (90%), R_f = 0.40 (4% methanol in chloroform), ^{1}H NMR (DMSO-d6): d = 3.00 (s, 6H, $2CH_3$), 4.05 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 6.85–8.15 (m, 8H, Ar-H), 8.37 (s, 1H, CH), 9.00 (brs, 1H, NH). Anal. Calcd for $C_{20}H_{20}N_6O_5S$: Calcd: C, 52.62; H, 4.42; N, 18.41. Found: C, 52.75; H, 4.55; N, 18.56.

General Procedures for the Reaction of Benzylidene Derivatives 10a-e and 11a-e with Acetic Anhydride to Afford Oxadiazoline Derivatives 12a-e and 13a-e

The mixture of benzylidene derivatives 10a-e and/or 11a-e (0.01 mole) and acetic anhydride (8 ml) was heated for 2 h (TLC) under reflux at 100°C. The mixture was poured onto crushed ice, and the product was filtered off, washed with water, and recrystallized from ethanol to afford oxadiazoline derivatives 12a-e and/or 13a-e, respectively, in 65–80% yields.

4-(nitrophenoxy)methyl)-2-phenyl-3-acetyl-1,3,4-oxadiazoline (12a)

White powder (80%), m.p. 165–167°C. R_f = 0.70 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.10 (s, 1H, $COCH_3$), 4.63 (s, 2H, CH_2), 6.65 (s, 1H, CH), 7.28–8.15 (m, 9H, Ar-H); MS m/z (%) 342 $(M+H)^+$. Anal. Calcd for $C_{17}H_{15}N_3O_5$: Calcd: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.75; H, 4.35; N, 12.25.

4-(nitrophenoxy)methyl)-2-(2-hydroxyphenyl)-3-acetyl-1,3,4-oxadiazoline (12b)

White powder (77%), m.p. 182–184°C. R_f = 0.70 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.10 (s, 1H, $COCH_3$), 4.63 (s, 2H, CH_2), 5.36 (brs, 1H, OH), 6.68 (s, 1H, CH), 6.88–8.15 (m, 8H, Ar-H); MS m/z (%) 368 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{15}N_3O_6$: Calcd: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.19; H, 4.33; N, 11.85.

4-(nitrophenoxy)methyl)-2-(4-nitrophenyl)-3-acetyl-1,3,4-oxadiazoline (12b)

Yellow powder (75%), m.p. 198–200°C. R_f = 0.70 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 1.98 (s, 1H, $COCH_3$), 4.60 (s, 2H, CH_2), 6.66 (s, 1H, CH), 7.28–8.12

(m, 8H, Ar-H); MS m/z (%) 388 $(M+2H)^+$. Anal. Calcd for $C_{17}H_{14}N_4O_7$: Calcd: C, 52.85; H, 3.65; N, 14.50. Found: C, 52.97; H, 3.73; N, 14.65.

4-(nitrophenoxy)methyl)-2-(3,4,5-trimethoxyphenyl)-3-acetyl-1,3,4-oxadiazoline (12d)

White powder (73%), m.p. 207–209°C. R_f = 0.70 (3% methanol in chloroform), ^{1}HNMR (DMSO-d6): δ = 2.10 (s, 1H, $COCH_3$), 3.85 (s, 9H, $3CH_3$), 4.60 (s, 2H, CH_2), 6.60 (s, 1H, CH), 6.85–8.10 (m, 6H, Ar-H). Anal. Calcd for $C_{20}H_{21}N_3O_8$: Calcd: C, 55.68; H, 4.91; N, 9.74. Found: C, 55.60; H, 4.75; N, 9.65.

4-(nitrophenoxy)methyl-2-(4-dimethylaminophenyl)-3-acetyl-1,3,4-oxadiazoline (12e)

Brown powder (80%), m.p. 232–234°C. R_f = 0.70 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.05 (s, 1H, $COCH_3$), 2.98 (s, 6H, $2CH_3$), 4.63 (s, 2H, CH_2), 5.36 (brs, 1H, OH), 6.58 (s, 1H, CH), 6.67–8.15 (m, 8H, Ar-H). Anal. Calcd for $C_{19}H_{20}N_4O_5$: Calcd: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.49; H, 5.43; N, 14.71.

4-(nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thiomethyl-2-phenyl-3- acetyl-1,3,4-oxadiazoline (13a)

White powder (65%), m.p. 230–232°C. R_f = 0.45 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.05 (s, 1H, $COCH_3$), 2.75 (s, 2H, CH_2), 5.36 (s, 2H, CH_2), 6.67 (s, 1H, CH), 7.22–8.15 (m, 9H, Ar-H); MS m/z (%) 455 (M^+). Anal. Calcd for $C_{20}H_{17}N_5O_6S$: Calcd: C, 52.72; H, 3.76; N, 15.38. Found: C, 52.85; H, 3.65; N, 15.20.

4-(nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thiomethyl-2-(2-hydroxyphenyl-3-acetyl-1,3,4-oxadiazoline (13b)

Yellow powder (70%), m.p. 220–223°C. R_f = 0.40 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): d = 2.10 (s, 1H, $COCH_3$), 2.85 (s, 2H, CH_2), 5.35 (brs, 1H, OH), 5.45 (s, 2H, CH_2), 6.67 (s, 1H, CH), 6.90–8.15 (m, 8H, Ar-H). Anal. Calcd for $C_{20}H_{17}N_5O_7S$: Calcd: C, 50.95; H, 3.63; N, 14.86. Found: C, 51.05; H, 3.70; N, 14.93.

4-(nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thiomethyl-2-(2-nitrophenyl-3-acetyl-1,3,4-oxadiazoline (13c)

Brown powder (72%), m.p. 264–266°C. R_f = 0.40 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.05 (s, 1H, $COCH_3$), 2.85 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.68 (s, 1H, CH), 7.25–8.10 (m, 8H, Ar-H). Anal. Calcd for $C_{20}H_{16}N_6O_8S$: Calcd: C, 48.00; H, 3.22; N, 16.79. Found: C, 48.15; H, 3.34; N, 16.88.

4-(nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thiomethyl-2-(3,4,5-trimethoxyphenyl)-3-acetyl-1,3,4-oxadiazoline (13d)

Yellow crystals (70%), m.p. 285–287°C. R_f = 0.45 (3% methanol in chloroform), ^{1}H NMR (DMSO-d6): δ = 2.05 (s, 1H, $COCH_3$), 2.85 (s, 2H, CH_2), 3.85 (s, 9H, $3CH_3$), 5.36 (s, 2H, CH_2), 6.62 (s, 1H, CH), 6.80–8.10 (m, 6H, Ar-H). Anal. Calcd for $C_{23}H_{23}N_5O_9S$: Calcd: C, 50.64; H, 4.25; N, 12.84. Found: C, 50.52; H, 4.13; N, 12.74.

4-(nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thio) methyl)-2-(4-dimethylaminophenyl)-3-acetyl-1,3,4-oxadiazoline (13e)

Yellow powder (65%), m.p. >300°C. R_f = 0.45 (3% methanol in chloroform), ^{1}HNMR (DMSO-d6): δ = 2.05 (s, 1H, $COCH_3$), 2.80 (s, 2H, CH_2), 3.10 (s, 6H, $2CH_3$), 5.36 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.85–8.15 (m, 8H, Ar-H). Anal. Calcd for $C_{20}H_{17}N_5O_6S$: Calcd: C, 52.72; H, 3.76; N, 15.38. Found: C, 52.85; H, 3.65; N, 15.20.

N-formyl-2-(4-nitrophenoxy)acetohydrazide (14a)

A mixture of hydrazide **3 (**2.11g, 10 mmole) and formic acid (15 ml) was heated for 15 h (TLC) under reflux. The solvent was evaporated under reduced pressure to give white powder in 80% yield, m.p. 243–245°C R_f = 0.71 (4% methanol in chloroform). IR spectra (KBr) (ν, cm^{-1}): 3336 (NH), 1645 (C=O), 1790 (CHO); ^{1}HNMR (DMSO-d_6): δ = 4.53 (s, 2H, CH_2), 7.30 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.20 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.33 (brs, 1H, NH), 8.50 (brs, 1H, NH), 9.10 (s, 1H, CHO); MS m/z (%) 241 $(M+2H)^+$. Anal. Calcd for $C_9H_9N_3O_5$: Calcd: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.33; H, 3.62; N, 17.77.

N-formyl-2-((5-((4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thioacetohydrazide (14b)

A mixture of hydrazide **7 (**3.25 g, 0.01 mole) and formic acid (30 ml) was heated for 24 h (TLC) under reflux. The solvent was evaporated under reduced pressure to afford white powder in 70% yield, m.p. >300°C R_f = 0.45 (4% methanol in chloroform). IR spectra (KBr) (ν, cm^{-1}): 3336 (NH), 1645 (C=O), 1790 (CHO); ^{1}HNMR (DMSO-d_6): d = 4.53 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 7.27 (d, 2H, *J* = 5.5 Hz, Ar-H), 8.30 (d, 2H, *J*= 5.5 Hz, Ar-H), 8.12 (brs, 1H, NH), 8.25 (brs, 1H, NH), 9.30 (s, 1H, CHO); MS m/z (%) 364 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{11}N_5O_6S$: Calcd: C, 40.79; H, 3.14; N, 19.82. Found: C, 40.43; H, 3.42; N, 19.56.

General Procedure for Preparation of α-aminophosphonate Derivatives 15a-e and 16a-e

A mixture of the *N*-formyl-2-(4-nitrophenoxy)acetohydrazide (14a) and/or N-formyl-2-((5-((4-nitrophenoxy)

methyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (14b), respectively (0.01 mole), triphenyl phosphite (10 mmole) and different amines (10 mmole) was dissolved in acetonitrile and then perchloric acid (1 ml) was added dropwise. The reaction mixture 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 15a-e and 16a-e, respectively, in 80–92% yields.

Diphenyl (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino(2-(2-(4-nitrophenoxy)acetyl) hydrazinyl methylphosphonate (15a)

Yellow powder in 80% yield, m.p. >300°C R_f = 0.71 (4% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): d = 2.28 (s, 3H, CH_3), 3.15 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.92–8.15 (m, 19H, Ar-H), 8.55 (brs, 1H, NH), 8.75 (brs, 1H, NH), 9.10 (brs, 1H, NH); MS m/z (%) 697 $(M+K)^+$. Anal. Calcd for $C_{32}H_{31}N_6O_8P$: Calcd: C, 58.36; H, 4.74; N, 12.76. Found: C, 58.47; H, 4.87; N, 12.65.

Diphenyl (2-(2-(4-nitrophenoxy)acetyl)hydrazinyl(p-tolylamino)methylphosphonate (15b)

Yellow oil in 85% yield, R_f = 0.71 (3% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 2.38 (s, 3H, CH_3), 4.53(s, 2H, CH_2), 6.45 (s, 1H, CH), 6.57–-8.15 (m, 18H, Ar-H), 8.35 (brs, 1H, NH), 8.55 (brs, 1H, NH), 8.84 (brs, 1H, NH). Anal. Calcd for $C_{28}H_{27}N_4O_7P$: Calcd: C, 59.79; H, 4.84; N, 9.96. Found: C, 59.85; H, 4.93; N, 10.05.

Diphenyl (4-methoxyphenyl)amino (2-(2-(4-nitrophenoxy) acetylhydrazinylmethylphosphonate (15c)

Yellow gum in 87% yield, R_f = 0.70 (3% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): d = 3.75 (s, 3H, OCH_3), 4.60 (s, 2H, CH_2), 6.55 (s, 1H, CH), 6.66–8.13 (m, 18H, Ar-H), 8.35 (brs, 1H, NH), 8.55 (brs, 1H, NH), 8.84 (brs, 1H, NH). Anal. Calcd for $C_{28}H_{27}N_4O_8P$: Calcd: C, 58.13; H, 4.70; N, 9.68. Found: C, 58.25; H, 4.84; N, 9.78.

Diphenyl (2-(2-(4-nitrophenoxy)acetylhydrazinyl (2-nitrophenyl)aminomethylphosphonate (15d)

Red oil in 85% yield, R_f = 0.72 (3% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1445 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 4.65 (s, 2H, CH_2), 6.68 (s, 1H, CH), 7.10–8.20 (m, 18H, Ar-H), 8.40 (brs, 1H, NH), 8.65 (brs, 1H, NH), 8.93 (brs, 1H, NH). Anal. Calcd for $C_{27}H_{24}N_5O_9P$: Calcd: C, 54.64; H, 4.08; N, 11.80. Found: C, 54.45; H, 4.00; N, 11.65.

Diphenyl (2-(2-(4-nitrophenoxy)acetyl)hydrazinyl) (pyridin-2-ylamino)methyl)phosphonate (15e)

Brown gum in 88% yield, R_f = 0.72 (3% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 4.63 (s, 2H, CH_2), 6.62 (s, 1H, CH), 6.69–8.12 (m, 18H, Ar-H), 8.42 (brs, 1H, NH), 8.69 (brs, 1H, NH), 8.98 (brs, 1H, NH). Anal. Calcd for $C_{26}H_{24}N_5O_7P$: Calcd: C, 56.83; H, 4.40; N, 12.75. Found: C, 56.91; H, 4.29; N, 12.90.

Diphenyl (1,5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1H-pyrazol-4-yl)amino(2-(2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetylhydrazinylmethylphosphonate (16a)

Brown powder in 88% yield, m.p. 267–269°C. R_f = 0.70 (4% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 5.38 (s, 2H, CH_2), 6.68 (s, 1H, CH), 6.92-8.15 (m, 19H, Ar-H), 8.45 (brs, 1H, NH), 8.79 (brs, 1H, NH), 9.05 (brs, 1H, NH). Anal. Calcd for $C_{35}H_{33}N_8O_9PS$: Calcd: C, 54.40; H, 4.30; N, 14.50. Found: C, 54.52; H, 4.35; N, 14.63.

Diphenyl-2-(2-(5-(4-nitrophenoxy)methyl)-1,3,4-oxadiazol-2-yl)thioacetylhydrazinyl(p-tolylamino) methylphosphonate (16b)

Red gum in 90% yield, R_f = 0.71 (3% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 5.40 (s, 2H, CH_2), 6.28 (s, 1H, CH), 6.45–8.15 (m, 18H, Ar-H), 8.50 (brs, 1H, NH), 8.75 (brs, 1H, NH), 8.97 (brs, 1H, NH). Anal. Calcd for $C_{31}H_{26}N_6O_8PS$: Calcd: C, 55.03; H, 4.32; N, 12.42. Found: C, 55.12; H, 4.45; N, 12.51.

Diphenyl (4-methoxyphenyl)amino (2-(2-5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl) thioacetylhydrazinylmethylphosphonate (16c)

White powder in 91% yield, m.p. 292–294°C. R_f = 0.71 (2% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 3.87 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 5.35 (σ, 2H, CH_2), 6.58 (s, 1H, CH), 7.00–8.20 (m, 18H, Ar-H), 8.55 (brs, 1H, NH), 8.85 (brs, 1H, NH), 8.96 (brs, 1H, NH); MS m/z (%) 692 (M^+). Anal. Calcd for $C_{31}H_{29}N_6O_9PS$: Calcd: C, 53.76; H, 4.22; N, 12.13. Found: C, 53.68; H, 4.15; N, 12.21.

Diphenyl-2-(2-(5-(4-nitrophenoxy)methyl-1,3,4-oxadiazol-2-yl)thio)acetyl)hydrazinyl)(2-nitrophenyl) aminomethylphosphonate (16d)

Yellow gum in 89% yield, R_f = 0.72 (2% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 4.15 (σ, 2H, CH_2), 5.35 (s, 2H, CH_2), 6.68 (s, 1H, CH), 7.10–8.15 (m, 18H, Ar-H), 8.65 (brs, 1H, NH), 8.95 (brs, 1H, NH), 9.20 (brs, 1H, NH). Anal. Calcd for $C_{30}H_{26}N_7O_{10}PS$: Calcd: C, 50.92; H, 3.70; N, 13.86. Found: C, 50.78; H, 3.62; N, 13.74.

Diphenyl (2-(2-(5-(4-nitrophenoxy)methyl)-1,3, 4-oxadiazol-2-yl)thio)acetyl)hydrazinyl)(pyridin-2-ylamino)methyl)phosphonate (16e)

Brown gum in 92% yield, R_f = 0.72 (5% methanol in chloroform). IR (KBr) (ν, cm^{-1}): 3340 (NH), 3080 (CH aromatic), 1640 (C=O), 1450 (CH_2); ^{1}H NMR (DMSO-d_6): δ = 4.00 (s, 2H, CH_2), 5.37 (s, 2H, CH_2), 6.60 (s, 1H, CH), 7.10–8.15 (m, 18H, Ar-H), 8.63 (brs, 1H, NH), 8.84 (brs, 1H, NH), 9.10 (brs, 1H, NH). Anal. Calcd for $C_{29}H_{26}N_7O_8PS$: Calcd: C, 52.49; H, 3.95; N, 14.78. Found: C, 52.58; H, 4.02; N, 14.91.

Evaluation of Cytotoxic Effects of Certain Synthesized Compounds

Cell line propagation

The cells were replicated in medium (DMEM) of Dulbecco's modified Eagle's completed with fetal bovine serum at 10% heat-inactivated HEPES buffer, 50 μg/ml gentamycin, and 1 % L-glutamine. The cells were maintained at 37°C in a moistened atmosphere with CO_2 (5%) and were subcultured 2 times a week.

Cytotoxicity evaluation using viability assay

For cytotoxicity assay, the cells were implanted in 96-well plate at a cell concentration of 1×10^4 cells per well in 100 μl of growth medium. Fresh medium containing different concentrations of the test sample was added after 24 h of implanting. The tested synthetic compounds were added to confluent cell monolayers dispensed into 96-well, in serial two-fold dilutions of flat-bottomed microtiter plates using a multichannel pipette. The microtiter plates were incubated at 37°C in moistened incubator with CO_2 (5%) for 48 h. For each concentration of the synthesized compound, three wells were used. Control cells were incubated without test compound and with or without DMSO. After incubation of the cells for at 37°C, various concentrations of synthesized compounds were added, and the incubation was continued for 24 h and viable cells yield was determined by colorimetric method.[16] After the end period of incubation, media were aspirated and 1% of crystal violet solution was added to each well for 30 min at least. The stain was separated and the plates were washed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, and then, the absorbance of the plates was measured after gently shaken on microplate reader (TECAN, Inc.), using a test wavelength 490 nm. All results were corrected for background absorbance detected in wells without added stain. Treatment samples were compared with the cell control in the absence of the synthesized compounds. All experiments were carried out in triplicate. The cell cytotoxic effect of each synthesized compound and 5-flurouracil as reference was calculated. The optical density was estimated with the microplate reader to determine the number of viable cells and the viability percentage was calculated as [1−(ODt/ODc)]×100%, where ODt is the mean optical density of wells treated with the synthesized samples and ODc is the mean optical density of untreated cells. The relation between eduring cells and drug concentration is colluted to get the survival curve of each tumor cell line after treatment with the specified compound. The 50% inhibitory concentration, the concentration required to cause toxic effects in 50% of intact cells, was evaluated from graphic plots of the dose-response curve for each concentration.[17]

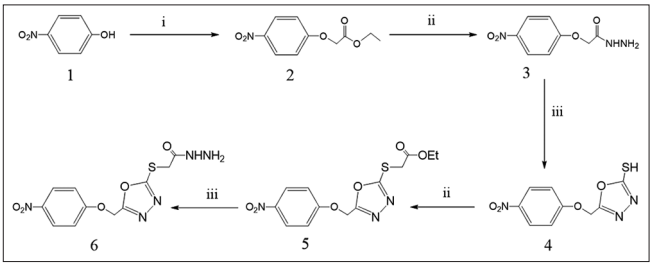
RESULTS

The findings of the present study are recorded in Tables 1-8 and Schemes 1-3.

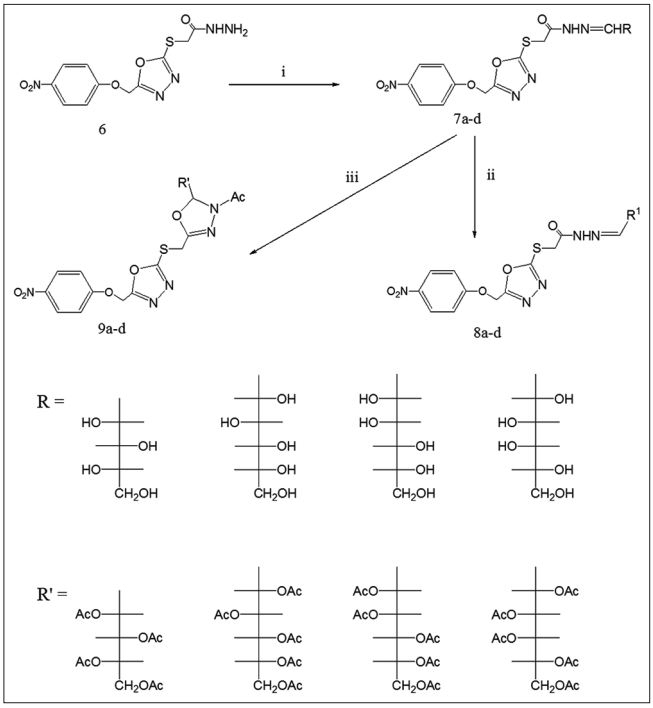
DISCUSSION

Chemistry

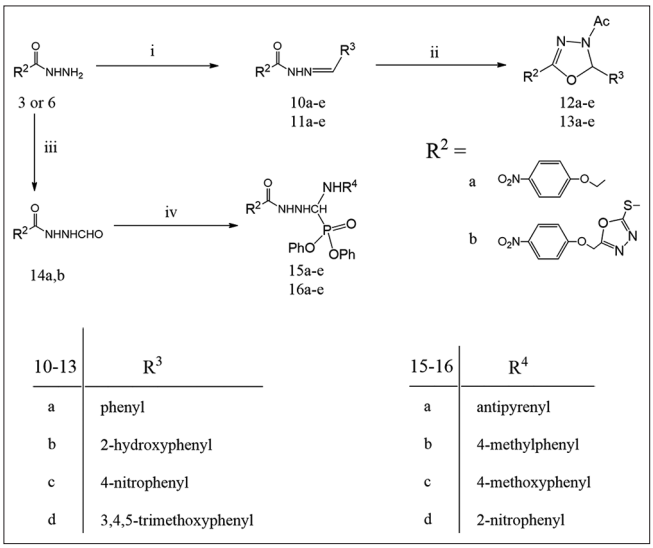
The hydrazide 3 is prepared by the method[18-21] using the reaction of *p*-nitrophenol with ethyl chloroacetate in the presence of pot. Carbonate to afford ester derivative 2 which is reacted with hydrazine hydrate to the product. The^{1}HNMR exhibits the appearance of CH_3CH_2 group of ester δ 2 at 1.24 (triplet) for CH_3, 4.15 (quartet) for CH_2, and 4.92 (singlet) of the methylene group while its IR showed the carbonyl group at 1738. The^{1}H NMR of the hydrazide 3 showed the disappearance of the ethyl group and appearance of $CONHNH_2$ group at δ 2.75 for (NH_2) and 8.33 for (NH), while its IR showed the hydrazide group at 3336 (NH), 3450 and 3270 (NH_2), and 1645 (C=O). The hydrazide is



Scheme 1: (i) $ClCH_2COOEt$, K_2CO3, acetone, reflux; (ii) N_2H_4. H_2O, EtOH, reflux; (iii) CS2, KOH, EtoH, reflux



Scheme 2: (i) RCHO, EtOH, AcOH, reflux; (ii) Ac_2O, pyridine, stirring; (iii) Ac_2O, reflux



10-13	R^3	15-16	R^4
a	phenyl	a	antipyrenyl
b	2-hydroxyphenyl	b	4-methylphenyl
c	4-nitrophenyl	c	4-methoxyphenyl
d	3,4,5-trimethoxyphenyl	d	2-nitrophenyl

Scheme 3: (i) R_3CHO, EtOH, AcOH, reflux; (ii) Ac_2O, reflux; (iii) HCOOH, reflux; (iv) R_4NH_2, $(PhO)_3P$, $HClO_4$, Me

cyclized by the reaction with CS_2 in the presence of KOH in ethanol under reflux to give oxadiazole derivative 4 which is followed by reaction with ethyl chloroacetate and then with hydrazine hydrate to afford oxadiazole ester derivative 5 and then oxadiazole hydrazide derivative 6, respectively. The ^{1}H NMR of oxadiazole derivative 4 showed the appearance of SH group at δ 13.15 and disappearance of hydrazide group ($CONHNH_2$) while the SH group is disappeared in ester derivative 5 and ethyl group is appeared at d 1.27 and 4.20 for CH_3 and CH_2, respectively. The ethyl group is disappeared in hydrazide derivative 6, while the protons of $CONHNH_2$ group appear at δ 3.53 for (NH_2) and 8.15 for (NH).

Table 1: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=38.8±5.4 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	8.42	91.58	0.26
250	16.31	83.69	0.45
125	28.45	71.55	0.71
62.5	40.27	59.73	2.95
31.25	53.12	46.88	2.24
15.6	79.88	20.12	1.68
7.8	94.06	5.94	0.69
3.9	99.34	0.66	0.12
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

Table 2: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=89.1±7.6 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	11.87	88.13	0.31
250	23.65	76.35	0.49
125	36.49	63.51	1.85
62.5	67.83	32.17	2.31
31.25	81.95	18.05	0.73
15.6	90.67	9.33	0.14
7.8	98.14	1.86	0.52
3.9	100	0	0
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

Table 3: Inhibitory activity against Hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=25.4±3.8 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	4.25	95.75	0.13
250	9.84	90.16	0.42
125	20.71	79.29	0.35
62.5	31.28	68.72	0.74
31.25	40.83	59.17	1.89
15.6	65.32	34.68	2.64
7.8	81.49	18.51	0.65
3.9	90.74	9.26	0.18
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

The oxadiazole hydrazide derivative 6 is reacted with monosaccharides (arabinose, glucose, mannose, and galactose) to form sugar hydrazone derivatives (7a-d) which

Table 4: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=90.2±8.1 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	9.50	86.39	0.37
250	20.12	80.14	0.49
125	25.73	75.24	0.81
62.5	37.45	55.37	2.85
31.25	50.14	40.78	1.94
15.6	89.38	24.22	1.54
7.8	95.08	12.98	1.00
3.9	98.64	10.86	0.76
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

Table 5: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=86.9±7.9 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	8.36	93.25	0.18
250	10.50	88.36	0.32
125	22.73	80.34	0.25
62.5	35.21	70.28	0.67
31.25	41.63	61.32	1.45
15.6	75.55	37.83	1.99
7.8	85.70	25.67	1.07
3.9	93.67	12.45	0.49
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

Table 6: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=248±19.6 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	31.78	68.22	0.96
250	49.56	50.44	2.38
125	80.42	19.58	3.86
62.5	95.13	4.87	0.75
31.25	99.76	0.24	0.11
15.6	100	0	0
7.8	100	0	0
3.9	100	0	0
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

Table 7: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=12.5±4.7 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	3.06	96.94	0.11
250	6.93	93.07	0.24
125	14.57	85.43	0.19
62.5	21.34	78.66	0.46
31.25	32.72	67.28	0.83
15.6	43.98	56.02	1.54
7.8	59.17	40.83	1.98
3.9	74.86	25.14	0.92
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

are acetylated by stirring in pyridine with (CH3CO)2O at room temperature to the acetylated sugar hydrazones derivatives (8a-d), respectively. IR spectra (cm−1) of sugar hydrazone derivatives 7a-d showed 3470–3420 for (OHs) and 3310–3270 for (NHs), while their1H NMR spectra showed the appearance of sugar protons between δ 2.76 and 7.35. IR spectra (cm-1) of acetylated sugar hydrazone derivatives 8a-d showed 3310–3270 for (NHs) and 1740–1730 (C=O) and disappear of the OH peak, while their1H NMR spectra showed the appearance of acetyl groups protons between δ 1.99 and 2.24. The sugar hydrazone derivatives (7a-d) are cyclized to oxadiazole C-nucleosides derivatives (9a-d) by heating with acetic anhydride at 90°C. IR spectra (cm-1) of acetylated C-nucleoside derivatives 9a-d showed 1745–1730 (C=O) and disappearance of the NH peak, while their1HNMR spectra showed the appearance of acetyl group protons between δ 2.01 and 2.24 and the oxadiazoline proton appears between d 5.85 and 5.95 (d, 1H, oxadiazoline H-5).

Both hydrazides 3 or/and 6 are allowed to react with different aldehydes to afford the corresponding imines 10a-e and 11a-e which are cyclized to oxadizolines 12a-e and 13a-e, respectively. 1H NMR spectra of 10a-e and 11a-e showed the presence of imine CH between d 8.30 and 8.80, while in compounds 12a-e and 13a-e, the oxadiazole proton appears between δ 6.58 and 6.68. The formulation of both 3 or/and 6 is carried out by refluxing with formic acid to afford 14a-b which are participated in three component reaction with amine and triphenyl phosphite in the presence of Lewis acid to afford phosphonate derivatives 15a-d and 16a-d. IR spectra (cm-1) of the formulated derivatives 14a-b showed 3336 for NH and 1645 C=O groups, while1H NMR showed the proton of the formyl group at δ 9.10 and 9.30 for 14a and 14 b, respectively. IR spectra of the phosphonate derivatives 15a-e and 16a-e showed the presence of amide carbonyl group around 1645/cm, while1H NMR showed the proton of P-CH between d 6.28 and 6.68.

Anticancer Activity

The anticancer activities of the synthesized nucleoside and phosphonate derivatives 3, 7a, 9d, 11d, 13b, 15e, and 16a

Table 8: Inhibitory activity against hepatocellular carcinoma cells was detected under these experimental conditions with IC_{50}=5.5±0.21 µg/ml

Sample conc. (µg/ml)	Viability %	Inhibitory %	SD (±)
500	1.55	98.45	0.55
250	5.37	94.63	0.19
125	9.60	91.40	0.13
62.5	16.47	83.53	0.35
31.25	24.42	75.58	0.61
15.6	46.22	53.78	1.62
7.8	52.16	47.84	0.74
3.9	75.44	24.66	0.93
0	100	0	0

IC_{50}: 50% inhibitory concentration, SD: Standard deviation

were tested against HepG-2 cell line.[22-25] 5-fluorouracil (5FU) was used in the experiment as a reference cytotoxic compound for HepG-2 cell line. The outline data in Tables 1, 3, 5 and 7 referred to the tested compounds 3, 9d, 13b, and 16a, respectively, showed a variable effect ranging from high to low activity against the tested HepG-2 cells. The outline data in Tables 2 and 4 referred to the tested compounds 7a and 11d, respectively, showed a variable effect ranging from moderate to low activity against the tested HepG-2 cells. The outline data in Table 6 referred to the tested compound 15e showed low activity against the tested HepG-2 cells. In general, compounds 16a and 9d were found to be the most potent derivatives against HepG-2 cells, where compounds 7a and 11d have moderate activities against HepG-2 cells. However, compound 15e has low activity against HepG-2 cells. The plurality of the synthesized sugar hydrazone and oxadiazoline derivatives shows strong-to-moderate cytotoxic effects against HepG-2 cells, may be due to the presence of (OH) or (COCH3) through increase the ability to form hydrogen bond. On the other hand, the synthesized phosphonate derivatives show high activity against HepG-2 cells, may be due to the presence of phosphorous atom. Hence, we showed that the strong connection was formed between these compounds and proteins. Compounds 9d and 16a exhibit the highest cytotoxicity against HepG-2 cells near to the reference anticancer drug 5FU.

CONCLUSION

In this work, new sugar hydrazones, arylidines, and α-aminophosphonates bearing 4-nitro phenol moiety were synthesized. The new synthesized compounds were tested against hepatocellular carcinoma and showed moderate-to-high activity. The 5FU was used as reference anticancer drug in this experiment.

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