

Research Article

# Synthesis of Novel 3-Acetyl N-methyl-2-Quinolone Derivatives with Expected Antimicrobial Activity

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## Abstract

A series of new 3-Acetyl N-Methyl-2-quinolones oxadiazoles derivatives were synthesized by reaction of 3-acetyl-4-hydroxy-1-methylquinolin-2(1H)-one **3** with ethylbromoacetate to produce compounds **4**. The hydrazinolysis of compound **4** with hydrazine hydrate afforded hydrazide compounds **5**. New Schiff bases **6** were obtained by condensation of compound **5** with different aryl aldehydes. The last step involves refluxing compound **6** with acetic anhydrides to give the corresponding 3-acetyl-N-methylquinolin-2-one oxadiazoles **7**. All the synthesized compounds were characterized on the basis of FT-IR, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR. The synthesized compounds have been evaluated for antimicrobial activity against Gram-positive and Gram-negative bacteria. Among sixteen synthesized novel compounds, in which five compounds (**7a**, **7b**, **7c**, **7e**, **7g**) exhibited promising Antimicrobial activity as compared to Trimethoprim (100µg/ml).

**Keywords:** Quinolines, Oxadiazoles, Antimicrobial activity.

## الخلاصة

لقد تم تحضير سلسلة جديدة من مشتقات 3-أسيتايل-N-مethyl-2-كوينولين أوكساديازول عن طريق تفاعل 3-أسيتايل-4-هيدروكسي-1-مethyl-2-كوينولينون مع أثيل برومو أسيتيت للحصول على مركبات **4**. تفاعل مركبات **4** مع الهيدرازين هيدريت ليعطي مركبات الهيدرازيد **5**. وتم الحصول على قواعد شف **6** جديدة بواسطة تكثيف مركبات **5** مع الديهايدرات أروماتية متنوعة. الخطوة الأخيرة تضمنت تفاعل غلق لمركبات قواعد شف مع أنهيدريد الحامض للحصول على مشتقات 3-أسيتايل-N-مethyl-2-كوينولين أوكساديازول. وتم تشخيص جميع المركبات المحضرة باستخدام تقنيات FT-IR, <sup>1</sup>H-NMR و <sup>13</sup>C-NMR. من بين ستة عشر درست الفعالية البكتيرية للمركبات الجديدة المحضرة تجاه بكتريا Gram-positive و Gram-negative. من بين ستة عشر من المركبات الجديدة المحضرة فقط خمسة مركبات (**7a**, **7b**, **7c**, **7e**, **7g**) أظهرت فعالية بيولوجية جيدة بالمقارنة مع دواء Trimethoprim (100µg/ml).

## Introduction

Synthesis of functionalized N-methylquinolin-2-one with acyl group in position 3 has found much interest because of their biological properties [1]. A wide spectrum of important pharmacological activities have been associated with 4-substituted 3-acylquinolin-2(1-methyl)-ones [2] [3] [4] [5] [6]. Several derivatives of this heterocyclic class are very interesting in biological activity and was found in many naturally occurring compounds, and also consider as useful intermediates for many medicinal products [7] [8] [9]. It had been reported that N-methyl derivatives of 4-hydroxyquinolin-2-one are possess significant biological activity [10] [11] [12], and many derivatives of 6-methylpyrano [3, 2-c] quinolinone are utilized as pharmaceutical active ingredients e. g. the famous alkaloids: veprisins and flindersins [13] [14].

Over the last few decades 2,5-disubstitued 1,3,4-oxadiazoles have received much attention because of their potential application as antioxidant, antibacterial, antitubercular and insecticidal agents [15] [16] [17] [18]. Herein, we report the first highly efficient total synthesis of seven novel 3-acetyl N-methyl-2-quinolones oxadiazoles derivatives. The chemical structures of the synthesized compounds **7** were characterized by spectroscopic techniques and confirmed. The antibacterial activities of the prepared compounds were investigated.

## Materials and Methods

All the chemicals and solvents used in this study were reagent grade and they are available from Sigma-Aldrich and Alfa-Aesar companies. Melting points were determined on a Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus),



Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected. The FT-IR spectra were obtained using Nicolet 205 FT-IR, Nicolet Protège 460 FT-IR. The  $^1\text{H-NMR}$  spectra were recorded on a Bruker AVANCE 250 II (built 2006), Bruker AVANCE 300 II (built 2007) spectrometry, using  $\text{CDCl}_3$  as solvent and TMS as internal standard. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light  $\lambda_{\text{max}}$  at 254 nm and  $\lambda_{\text{max}}$  at 365 nm. Solutions were evaporated under diminished pressure unless otherwise stated. 3-acetyl-4-hydroxy-1-methylquinolin-2(1H)-one **3** was obtained according to ref. [19].

#### Preparation of compounds 4-7 Preparation of ethyl 2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetate (**4**):

A stirred mixture of 3-acetyl-4-hydroxy-1-methylquinolin-2(1H)-one **3** (0.1 mol), anhydrous potassium carbonate (0.1 mol), and ethyl bromoacetate (0.12 mol) was heated under reflux in dry acetone (25ml) for 12 h. The resulting solution was allowed to cool to room temperature, and the produced precipitate was filter off, washed thoroughly with acetone, and then dried under vacuum. Yield 90%; M. p. 210 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1735 ( $\text{C}=\text{O}_{\text{ester}}$ ), 1715, 1692 ( $\text{C}=\text{O}_{\text{ketone}}$ ), 1285 ( $\text{C}-\text{O}_{\text{ester}}$ ).  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.27 (t, 3H,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3_{\text{ketone}}$ ), 3.52 (s, 3H, N- $\text{CH}_3$ ), 4.25 (q, 2H,  $\text{CH}_2$ ,  $J$  = 7.3 Hz), 5.16 (s, 2H,  $\text{OCH}_2$ ), 7.23-7.30 (m, 3H, ArH), 7.49-7.52 (m, 1H, ArH).  $^{13}\text{C NMR}$  (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.0, 30.9, 33.1 (3 $\text{CH}_3$ ), 61.0, 65.3 ( $\text{CH}_2$ ), 102.2, 106.2 (C), 120.6, 124.8, 126.3, 128.3 (CH), 129.3, 131.0, 156.9 (C), 167.7 ( $\text{CO}_{\text{ester}}$ ), 206.9 (CO).

#### Preparation of 2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)acetohydrazide (**5**):

A solution of compound **4** (0.05 mol) and 80% hydrazine hydrate (0.03 mol) in (25ml) methanol was stirred for 10 h at room temperature. After concentrating the reaction mixture under pressure the residue solid mass washed with methanol and then recrystallized using absolute ethanol to give a yellow solid of compound (**5**). Yield 88%; M. p. : 225 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1745, 1705, 1685 ( $\text{C}=\text{O}$ ), 3367-3462 ( $-\text{NHNH}_2$ ).  $^1\text{H NMR}$

(250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.26 (s, 3H,  $\text{CH}_3$ ), 3.56 (s, 3H, N- $\text{CH}_3$ ), 4.25 (s, 2H,  $\text{NH}_2$ ), 4.95 (s, 2H,  $\text{OCH}_2$ ), 7.21 (d, 1H,  $J$  = 8.2 Hz, ArH), 7.49-7.53 (m, 3H, ArH), 8.01 (s, 1H, NH).  $^{13}\text{C NMR}$  (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.8, 34.1 (2 $\text{CH}_3$ ), 63.0 ( $\text{CH}_2$ ), 102.2, 107.4 (C), 113.5, 124.7, 125.6, 128.7 (CH), 142.5, 150.8, 155.7, 157.6 (C), 207.5 (CO).

#### Preparation of (E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(arylidene)acetohydrazide (**6**):

A stirred solution of hydrazide (**5**) (0.05 mol) and appropriate substituted aldehyde (0.052) in ethanol (25ml) was refluxed for 6 h at boiling temperature. The obtained brownish solution was poured in cold water (50ml). The produced solid was filtered and recrystallized with ethanol.

(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(4-bromobenzylidene)acetohydrazide (**6a**). Yield: 80%; M. p. 230 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1740, 1708, 1695 ( $\text{C}=\text{O}$ ), 1430 ( $\text{C}=\text{N}$ ), 3210 (NH).  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.27 (s, 3H,  $\text{CH}_3$ ), 3.43 (s, 3H, N- $\text{CH}_3$ ), 4.86 (s, 2H,  $\text{OCH}_2$ ), 6.25 (s, 1H, N=CH), 7.25-7.29 (m, 3H, ArH), 7.49-7.53 (m, 3H, ArH), 8.25-8.39 (m, 2H, ArH), 9.99 (s, 1H, NH).  $^{13}\text{C NMR}$  (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 30.9, 34.5 (2 $\text{CH}_3$ ), 67.7 ( $\text{CH}_2$ ), 100.4, 112.2 (C), 120.4, 122.3, 123.5 (CH), 125.9 (C), 126.6, 127.6, 128.5, 129.3, 129.6 (CH), 130.6, 135.7 (C), 136.0 (CH), 145.3, 145.8, 146.5 (C), 206.2 (CO).

(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(4-chlorobenzylidene)acetohydrazide (**6b**). Yield: 75%; M. p. 205 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1735, 1705, 1692 ( $\text{C}=\text{O}$ ), 1530 ( $\text{C}=\text{N}$ ), 3211 (NH).  $^1\text{H NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.36 (s, 3H,  $\text{CH}_3$ ), 3.53 (s, 3H, N- $\text{CH}_3$ ), 4.67 (s, 2H,  $\text{OCH}_2$ ), 6.29 (s, 1H, N=CH), 7.12 (d, 2H,  $J$  = 8.1 Hz, ArH), 7.28-7.38 (m, 3H, ArH), 7.39-7.67 (m, 3H, ArH), 9.85 (s, 1H, NH).  $^{13}\text{C NMR}$  (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.1, 30.8 (2 $\text{CH}_3$ ), 67.9 ( $\text{CH}_2$ ), 112.1, 122.1 (C), 123.2, 124.2, 125.0, 126.7, 128.3, 129.3, 130.1, 130.2 (CH), 135.5, 135.8, 135.9 (C), 137.5 (CH), 144.3, 144.6, 159.2 (C), 206.1 (CO).

(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(naphthalen-1-

*ylmethylene)acetohydrazide (6c)*. Yield: 82%; M. p.222 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1748, 1705, 1690 (C=O), 1485 (C=N), 3222 (NH).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.28 (s, 3H,  $\text{CH}_3$ ), 3.53 (s, 3H, N- $\text{CH}_3$ ), 4.78 (s, 2H,  $\text{OCH}_2$ ), 8.79 (s, 1H, N=CH), 7.13 (d, 2H,  $J$  = 8.2Hz, ArH), 7.28-7.42 (m, 3H, ArH), 7.51-7.72 (m, 3H, ArH), 7.82-7.93 (m, 3H, ArH), 9.87 (s, 1H, NH).<sup>13</sup>C NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.9, 31.1 (2 $\text{CH}_3$ ), 67.6 ( $\text{CH}_2$ ), 103.0, 112.1 (C), 120.5, 121.9, 123.4, 123.6, 124.6, 128.3, 129.3, 130.1 (CH), 131.2, 135.5 (C), 136.0 (CH), 142.4, 144.2 (C), 147.3 (CH), 156.8, 158.9, 167.3 (C), 207.3 (CO).

*(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(3,4-dimethoxybenzylidene)acetohydrazide (6d)*. Yield: 77%; M. p.245 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1750, 1710, 1695 (C=O), 1480 (C=N), 3100 (NH).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.27 (s, 3H,  $\text{CH}_3$ ), 3.43 (s, 3H, N- $\text{CH}_3$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 5.12 (s, 2H,  $\text{OCH}_2$ ), 7.25 (d, 2H,  $J$  = 8.1Hz, ArH), 7.26-7.29 (m, 3H, ArH), 7.49-7.52 (m, 2H, ArH), 8.43 (s, 1H, N=CH), 9.93 (s, 1H, NH).<sup>13</sup>C NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.7, 31.1 (2 $\text{CH}_3$ ), 56.2 (2 $\text{OCH}_3$ ), 67.2 ( $\text{CH}_2$ ), 105.8 (C), 112.1, 123.0, 123.4, 123.5, 126.1, 126.2, 127.9 (CH), 128.3, 129.3 (C), 130.6 (CH), 135.4, 136.0, 145.5, 147.3, 159.8, 167.2 (C), 205.3 (CO).

*(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(4-hydroxybenzylidene)acetohydrazide (6e)*. Yield: 80%; M. p.235 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1755, 1712, 1693 (C=O), 1510 (C=N), 3210 (NH).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.41 (s, 3H,  $\text{CH}_3$ ), 3.64 (s, 3H, N- $\text{CH}_3$ ), 5.14 (s, 2H,  $\text{OCH}_2$ ), 5.74 (s, 1H, OH), 7.09 (d, 2H,  $J$  = 8.3Hz, ArH), 7.32-7.39 (m, 3H, ArH), 7.58-7.64 (m, 3H, ArH), 8.17 (s, 1H, N=CH), 9.84 (s, 1H, NH).<sup>13</sup>C NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.7, 33.6 (2 $\text{CH}_3$ ), 65.4 ( $\text{CH}_2$ ), 105.1, 112.3 (C), 119.2, 122.3, 122.6, 123.4, 123.5 (CH), 127.3 (C), 127.4, 128.0 (2CH), 128.9 (C), 130.6 (CH), 135.1, 137.5, 157.6, 159.3 (C), 205.1 (CO).

*(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(4-*

*methylbenzylidene)acetohydrazide (6f)*. Yield: 82%; M. p.200 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1755, 1712, 1696 (C=O), 1510 (C=N), 3210 (NH).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.28 (s, 3H,  $\text{CH}_3$ ), 2.41 (s, 3H,  $\text{CH}_3$ ), 3.77 (s, 3H, N- $\text{CH}_3$ ), 5.21 (s, 2H,  $\text{OCH}_2$ ), 6.96-6.98 (m, 3H, ArH), 7.05-7.06 (m, 2H, ArH), 7.22-7.27 (m, 3H, ArH), 8.33 (s, 1H, N=CH), 9.81 (s, 1H, NH).<sup>13</sup>C NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.7, 27.5, 30.5 (3 $\text{CH}_3$ ), 63.8 ( $\text{CH}_2$ ), 103.1, 112.1, 114.1 (C), 120.5, 121.8, 123.4, 123.6, 124.7, 127.7, 127.8 (CH), 129.4, 130.1, 130.6 (C), 131.2 (CH), 142.4, 156.8, 158.2 (C), 206.4 (CO).

*(E)-2-((3-acetyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)oxy)-N'-(4-nitrobenzylidene)acetohydrazide (6g)*. Yield: 75%; M. p.215 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1760, 1715, 1689 (C=O), 1558 (C=N), 3225 (NH).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.27 (s, 3H,  $\text{CH}_3$ ), 3.63 (s, 3H, N- $\text{CH}_3$ ), 4.92 (s, 2H,  $\text{OCH}_2$ ), 7.04-7.12 (m, 3H, ArH), 7.32 (d, 2H,  $J$  = 8.5Hz, ArH), 7.33-7.52 (m, 1H, ArH), 7.53-7.77 (m, 2H, ArH), 8.37 (s, 1H, N=CH), 9.67 (s, 1H, NH).<sup>13</sup>C NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.6, 30.5 (2 $\text{CH}_3$ ), 65.5 ( $\text{CH}_2$ ), 103.1, 112.3 (C), 121.7, 122.2, 123.5, 123.6, 125.7, 126.7, 128.4, 128.9 (CH), 129.3, 129.6 (C), 130.5 (CH), 135.6, 136.1, 142.1, 159.2 (C), 207.4 (CO).

### Preparation of 3-acetyl-4-((4-acetyl-5-substituted-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one (7)

A mixture of compound 6 (0.001), and acetic anhydride (10ml), was stirred for 15 min., and then heated under reflux for 12 h. The hot reaction mixture was poured onto ice water (10ml), and the produced precipitate was filtered off, washed many times with water, and then recrystallized from ethanol and dried [20].

*3-acetyl-4-((4-acetyl-5-(4-bromophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one (7a)*. Yield: 75%; M. p.245 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1715, 1705, 1690 (C=O), 1645 (C=N), 1445 (N-N), 1250 (C-O-C).<sup>1</sup>H NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.36 (s, 3H,  $\text{CH}_3$ ), 2.55 (s, 3H,  $\text{CH}_3$ ), 3.94 (s, 3H, N- $\text{CH}_3$ ), 5.67 (s, 2H,  $\text{OCH}_2$ ), 6.29 (s, 1H, H<sup>5</sup>), 7.11 (d,



2H,  $J = 8.1$  Hz, ArH), 7.25-7.29 (m, 3H, ArH), 7.40-7.67 (m, 3H, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 25.5, 29.2, 30.3$  (3CH<sub>3</sub>), 67.2 (CH<sub>2</sub>), 85.4 (CH), 103.0, 112.2 (C), 114.2 (CH), 121.7 (C), 122.2, 123.4, 123.5, 125.7, 126.6, 128.9, 129.4 (CH), 129.7, 130.5, 130.7, 142.1, 158.2, 159.2 (C), 207.2 (CO).

*3-acetyl-4-((4-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7b). Yield: 80%; M. p. 230 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1720, 1701, 1684 (C=O), 1595 (C=N), 1450 (N-N), 1240 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.27$  (s, 3H, CH<sub>3</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 4.06 (s, 3H, N-CH<sub>3</sub>), 5.56 (s, 2H, OCH<sub>2</sub>), 6.25 (s, 1H, H<sup>5'</sup>), 7.15-7.38 (m, 3H, ArH), 7.49-7.75 (m, 3H, ArH), 8.25-8.43 (m, 2H, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 21.0, 29.2, 30.8$  (3CH<sub>3</sub>), 67.4 (CH<sub>2</sub>), 86.0 (CH), 103.0, 112.2 (C), 121.7 (CH), 122.2 (C), 123.5, 123.8, 125.7, 126.7, 128.5, 129.0, 129.3 (CH), 129.7, 130.5, 135.6, 136.0, 142.1, 159.2 (C), 206.2 (CO).

*3-acetyl-4-((4-acetyl-5-(naphthalen-1-yl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7c). Yield: 72%; M. p. 232 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1715, 1707, 1691 (C=O), 1650 (C=N), 1480 (N-N), 1250 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.28$  (s, 3H, CH<sub>3</sub>), 2.55 (s, 3H, CH<sub>3</sub>), 3.78 (s, 3H, N-CH<sub>3</sub>), 5.55 (s, 2H, OCH<sub>2</sub>), 6.25 (s, 1H, H<sup>5'</sup>), 7.09-7.25 (m, 3H, ArH), 7.29-7.39 (m, 3H, ArH), 7.40-7.63 (m, 3H, ArH), 7.83 (d, 2H,  $J = 8.1$  Hz, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 25.4, 29.2, 30.3$  (3CH<sub>3</sub>), 67.2 (CH<sub>2</sub>), 85.2 (CH), 103.0, 112.2 (C), 114.0, 121.7, 122.2, 123.5, 123.6, 125.7, 126.6, 128.9, 129.4, 129.8, 130.5 (CH), 130.7, 142.0, 145.3, 145.8, 146.9, 158.2, 159.2 (C), 207.0 (CO).

*3-acetyl-4-((4-acetyl-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7d). Yield: 80%; M. p. 240 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1718, 1700, 1690 (C=O), 1655 (C=N), 1420 (N-N), 1195 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.29$  (s, 3H, CH<sub>3</sub>), 2.53 (s, 3H, CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, N-CH<sub>3</sub>), 5.52 (s, 2H, OCH<sub>2</sub>), 6.43 (s, 1H, H<sup>5'</sup>), 7.25-7.26 (m, 2H, ArH), 7.27-7.29 (m, 3H, ArH), 7.49-7.52 (m, 2H, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 23.4,$

29.2, 30.3 (3CH<sub>3</sub>), 55.2-55.4 (2OCH<sub>3</sub>), 67.2 (CH<sub>2</sub>), 86.4 (CH), 102.4, 112.1 (C), 114.1, 120.2, 121.9, 123.5, 123.6, 124.8, 127.7 (CH), 129.4, 130.1, 130.5, 131.2, 147.2, 157.5, 158.2, 159.1 (C), 207.2 (CO).

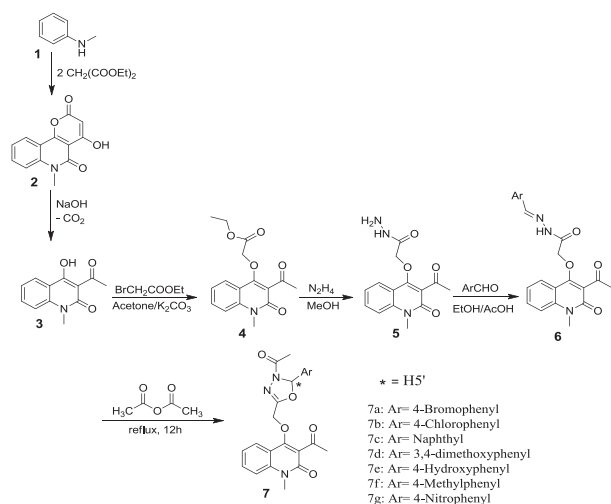
*3-acetyl-4-((4-acetyl-5-(4-hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7e). Yield: 70%; M. p. 230 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1715, 1706, 1690 (C=O), 1651 (C=N), 1401 (N-N), 1200 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.24$  (s, 3H, CH<sub>3</sub>), 2.63 (s, 3H, CH<sub>3</sub>), 3.98 (s, 3H, N-CH<sub>3</sub>), 5.62 (s, 2H, OCH<sub>2</sub>), 5.98 (s, 1H, OH), 6.33 (s, 1H, H<sup>5'</sup>), 7.11 (d, 2H,  $J = 8.3$  Hz, ArH), 7.38-7.39 (m, 3H, ArH), 7.56-7.64 (m, 3H, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 23.9, 29.2, 30.4$  (3CH<sub>3</sub>), 67.2 (CH<sub>2</sub>), 85.3 (CH), 103.2, 112.2 (C), 114.1, 120.3, 122.3, 123.5, 126.5, 127.6, 129.5 (CH), 130.5, 130.8, 145.7, 146.5, 146.9, 158.2, 159.2 (C), 206.2 (CO).

*3-acetyl-4-((4-acetyl-5-(p-tolyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7f). Yield: 65%; M. p. 215 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1718, 1702, 1689 (C=O), 1665 (C=N), 1480 (N-N), 1250 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.33$  (s, 3H, CH<sub>3</sub>), 2.52 (s, 3H, CH<sub>3</sub>), 3.57 (s, 3H, CH<sub>3</sub>), 4.08 (s, 3H, N-CH<sub>3</sub>), 5.67 (s, 2H, OCH<sub>2</sub>), 6.29 (s, 1H, H<sup>5'</sup>), 7.09-7.25 (m, 3H, ArH), 7.28-7.40 (m, 3H, ArH), 7.65 (d, 2H,  $J = 8.2$  Hz, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 21.9, 25.4, 29.2, 31.5$  (4CH<sub>3</sub>), 67.4 (CH<sub>2</sub>), 85.9 (CH), 102.4, 112.1 (C), 120.2, 121.9, 123.5, 123.6, 124.4, 126.5, 127.7, 128.5 (CH), 128.7, 130.2, 131.2, 138.5, 147.3, 157.5, 158.9 (C), 207.9 (CO).

*3-acetyl-4-((4-acetyl-5-(4-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-1-methylquinolin-2(1H)-one* (7g). Yield: 77%; M. p. 205 °C. IR (KBr) [ $\nu$ ,  $\text{cm}^{-1}$ ]: 1715, 1705, 1690 (C=O), 1615 (C=N), 1450 (N-N), 1221 (C-O-C).  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.33$  (s, 3H, CH<sub>3</sub>), 2.77 (s, 3H, CH<sub>3</sub>), 3.98 (s, 3H, N-CH<sub>3</sub>), 5.61 (s, 2H, OCH<sub>2</sub>), 6.41 (s, 1H, H<sup>5'</sup>), 6.96-6.98 (m, 3H, ArH), 7.07 (d, 2H,  $J = 8.2$  Hz, ArH), 7.22-7.27 (m, 3H, ArH).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ):  $\delta = 24.7, 29.2, 31.5$  (3CH<sub>3</sub>), 67.7 (CH<sub>2</sub>), 85.0 (CH), 103.0, 112.3 (C), 120.3, 121.9, 123.5, 123.6, 124.3, 126.5, 127.8, 128.5 (CH), 128.7, 130.1, 131.2, 138.6, 147.4, 156.9, 158.9 (C), 207.2 (CO).

## Results and Discussion

The synthesis of the desired compounds was accomplished according to the representation scheme 1.



Scheme 1: Total synthesis of 3-acetyl-N-methylquinolin-2-one oxadiazoles 7.

The starting material 3-acetyl-4-hydroxy-1-methylquinolin-2(1H)-one **3** was obtained from known method from aniline **1** and diethyl malonate via the pyronoquinolone **2** and subsequent ring opening with sodium hydroxide followed by spontaneous decarboxylation [19]. Compound **4** was prepared in 90% yield by refluxing ethylbromoacetate with compound **3** in anhydrous acetone in the presence of anhydrous potassium carbonate. It was observed that the broad band belong to the OH stretching in compound **3** was disappeared in IR spectrum of compound **4** and also signal disappearance of OH proton in <sup>1</sup>H-NMR spectrum of compound **4**. Hydrazinolysis of compound **4** with 80% hydrazine hydrate in methanol at room temperature afforded hydrazide compounds **5** in good yield. The FT-IR spectrum of compound **5** exhibited absorption bands in the region 3342.7-3201.8 cm<sup>-1</sup> (belong to hydrazide NH-NH<sub>2</sub>) and 1645.7 (amide carbonyl stretching). The <sup>1</sup>H-NMR spectra showed a singlet due to the -NH proton at δ 8.08 ppm. The -OCH<sub>2</sub> methylene protons appeared as singlet at 4.94 ppm [20]. Heating hydrazide compound **5** with different aryl aldehydes in absolute ethanol in the presence of a

catalytic amount of glacial acetic acid for 5-6 h afforded the corresponding compounds **6**<sub>a-g</sub>. The evidence for formation of Schiff base is the disappearance of a significant two bands at 3332 and 3150 cm<sup>-1</sup> which could be attributed to asymmetric and symmetric stretching vibrations of NH<sub>2</sub> group in compound **5**, and the <sup>1</sup>H-NMR showed disappearance of singlet (NH<sub>2</sub>) protons at 4.25 ppm, and displayed a singlet (N=CH) proton at 6.25 ppm in compounds **6**. In the last step for synthesis of target compounds, the compounds **6**<sub>a-g</sub> then refluxed with acetic anhydride for 8-10 h to give the corresponding substituted 3-acetyl-N-methylquinolin-2-one oxadiazoles **7**<sub>a-g</sub> in good yields. All the new substituted derivatives of oxadiazoles compounds **7** have been characterized by FT-IR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR spectroscopy, to elucidate their structures. The <sup>1</sup>H-NMR spectrum of compounds **7**<sub>a-g</sub> exhibited disappearance of singlet N-H proton at 9.8 ppm, and instead, it displayed a methyl protons of the additional acyl group connected to oxadiazole ring appear as a singlet at δ 2.65 ppm. The aromatic protons (both quinolinone and oxadiazolinic) are observed between 7.05 and 7.96 ppm.

**Antimicrobial activity** [21] [22] [23] [24]: All the synthesized compounds **4-7** have been screened in vitro for their antibacterial activity against gram-positive bacteria *Staphylococcus aureus* (NTCC 11632), *Bacillus subtilis* (ATCC 60511), gram-negative bacteria *Escherichia coli* (ATCC 10536), and the fungus *Candida albicans* (ATCC 2501) at 100 µg/ml concentration by cup-plate agar diffusion method using dimethylsulfoxide as a solvent and using trimethoprim as a reference. After 24 and 48h of incubation at 37<sup>o</sup>±1, the antimicrobial activity was determined by measuring the zones of inhibition in mm. The results are summarized in Table (1).

Table 1: In vitro antimicrobial activity of the synthesized compounds at a concentration of 100 µg/ml (zone of inhibition in mm).

Compounds	Zone of inhibition		
	Gram-positive bacteria	Gram-negative	Fungus

			bacteria	
	S. aureus	B. subtilis	E. coli	C. albicans
4	11	07	10	11
5	10	-	12	-
6a	15	17	20	-
6b	11	13	18	-
6c	16	15	21	14
6d	14	12	19	13
6e	09	12	22	-
6g	16	-	18	12
6f	15	-	17	11
7a	21	22	31	18
7b	20	22	30	17
7c	22	24	32	19
7d	16	19	19	-
7e	22	23	31	20
7f	-	-	15	09
7g	21	24	31	20
Trimethoprim	23	26	34	21

-No inhibition zone

When we examine the data of inhibition zone of all compounds against gram-positive bacteria, we observed that compounds **4,5,6<sub>a-g</sub>** showed poor activity, while compounds **7<sub>a-g</sub>** showed higher activity against the same bacteria. We noted that compounds **4, 5, 6<sub>a-g</sub>** also exhibited a moderate activity against E. coli bacteria compared with compounds **7<sub>a-g</sub>** which appeared a potent bacterial growth inhibition. In the same context, inspection the biological activity results of all synthesized compounds against C. albicans we found similarly that only compounds **7<sub>a-c, e, g</sub>** showed very good activity compared to the other. The professional antimicrobial activity of compounds

**7<sub>a-c, e, g</sub>**, we can be attributed may be to the presence of oxadiazole fragments in the structure of these compounds.

## Conclusions

In conclusion, we developed a convenient and high yielding methodology for the synthesis of novel 3-acetyl N-methyl-2-quinolinone oxadiazoles compounds and evaluated for antimicrobial activity. The antibacterial test against gram-positive and gram-negative bacteria performed on the obtained products showed that compounds (**7a, 7b, 7c, 7g**) possess a potent activity as compared to Trimethoprim. The presence of oxadiazole fragments with electron poor substituents in the structure of these compounds may be play a main role of their antimicrobial activity. Suitable molecular modification of these compounds probably generate a powerful antimicrobial agents in future.

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