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Novel heterocyclic derivatives of pyrano[3,2-*c*]quinolinone from 3-(1-ethy1-4-hydroxy-2-oxo-2(1*H*)-quinolin-3-yl)-3-oxopropanoic acid

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ABSTRACT

3-(1-Ethyl-4-hydroxy-2-oxo-2(1*H*)-quinolin-3-yl)-3-oxopropanoic acid (**2**) has been synthesized. The chemical behaviour of *β*-ketoacid **2** was studied towards condensation reactions with salicylaldelyde, 2-hydroxy-1-naphthaldehyde, 1-phenyl-4-hydroxy-2-oxo-quinoline-3-carboxaldehyde, 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxaldehyde, 2-amino-3-formylchromone and its 8-allyl analog, 3-cyanochromone and its 8-allyl analog. Structures of the newly synthesized products have been deduced from their elemental analysis and spectral data.

1. Introduction

4-Hydroxyquinolin-2(1*H*)-ones represents one of the most important class of heterocycles possessing wide spectrum of biological activities [1-8]. Heating *N*-ethylaniline with two equivalent diethylmalonate gave 4-hydroxypyrano[3,2-*c*]-quinolin-2(1*H*)one (**1**) in one-pot double cyclocondensation process [9,10]. The pyranoquinolinone **1** is a valuable intermediate for the synthesis of a variety of quinolin-2-ones bearing various functional groups in position 3 *via* chemical degradation of pyrone ring in compound **1**. For example, degradation of **1** in boiling 2N sodium hydroxide aqueous solution yielded 1-ethyl-3-acetyl-4-hydroxyquinolin-2(1*H*)-one through pyrone ring opening, followed by decarboxylation [11,12]. In continuation to previous research on 4-hydroxyquinolin-2(1*H*)-ones [13-18], the present paper reports the synthesis of the new 3-(1-ethy1-4-hydroxy-2-oxo-2(1*H*)-quinolin-3-yl)-3-oxo-propanoic acid (**2**) and the study of its chemical reactivity towards some *ortho*-hydroxyaldehydes and *ortho*-aminoaldehydes, in search of new quinolinone derivatives of potential biological activity.

2. Experimental

2.1. Instrumentation

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on a Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR spectra were measured on Gemini-200 (200 MHz) and/or Mercury-300BB (300MHz) spectrometers, using DMSO-d_6 as solvent and TMS (δ) as internal standard. ^{13}C NMR spectra were measured on a Mercury-300BB (75MHz) spectrometer, using DMSO-d_6 as solvent and TMS (δ) as internal standard. Mass spectra were obtained using a GC-2010 Shimadzu Gas chromatography-mass spectrometer (70 eV) instrument. Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

2.2. 3-(1-Ethy1-4-hydroxy-2-oxo-2(1H)-quinolin-3-yl)-3-oxopropanoic acid (2)

A solution of 6-ethyl-4-hydroxy-2*H*-pyrano[3,2-*c*]quino line-2,5(6*H*)-dione (**1**) (25.7 g, 100 mmol) in 1N sodium hydroxide aqueous solution (250 mL) was warmed at 40–50 °C for 30 min (Scheme 1). The solution so formed was filtered and the clear solution was acidified with 10% HCl. The precipitate so formed was filtered, washed several times with water, air dried and crystallized from acetic acid to give **2** as yellow crystals. M.p.: 226 °C. Yield: 21 g, 76%. IR (KBr, cm^{-1}): 3429 (OH), 3220 (OH), 3074 ($CH_{arom.}$), 2978, 2934, 2869 (CH_3, CH_2), 1727 ($C{=}O_{carboxy}$), 1673 ($C{=}O_{quinolinone}$), 1613 ($C{=}O_{ketone}$). ^1H NMR (DMSO-d_6, δ): 1.26 (t, 3H, *J*=6.8 Hz, CH_2CH_3), 4.35 (q, 2H, *J*=6.8 Hz, CH_2CH_3), 5.56 (s, 2H, CH_2), 7.48 (d, 1H, *J*=6.8 Hz, H-8), 7.84 (m, 2H, H-6 and H-7), 8.06 (d, 1H, *J*= 8.0 Hz, H-5), 12.02 (br, 1H exchangeable with D_2O, $OH_{carboxy}$), 13.41 (br, 1H exchangeable with D_2O, $OH_{quinolinone}$). M/z (relative intensity): 257 ($M^+ - H_2O$), 229 (100), 214 (9), 200 (79), 184 (11), 158 (12), 118 (6), 104 (4), 77 (3). Anal. Calcd for $C_{14}H_{13}NO_5$ (275.26): C, 61.06; H, 4.76; N, 5.09%. Found C, 61.31; H, 4.99; N, 5.31%.

2.3. 2-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)carbonyl)]-3-(2-hydroxy phenyl)-prop-2-enoic acid (3)

A mixture of *β*-ketoacid **2** (0.55 g, 2 mmol) and salicylaldehyde (0.21 mL, 2 mmol), in glacial acetic acid (10

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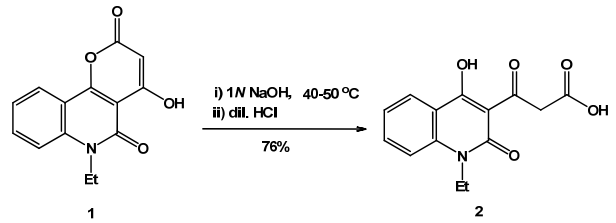
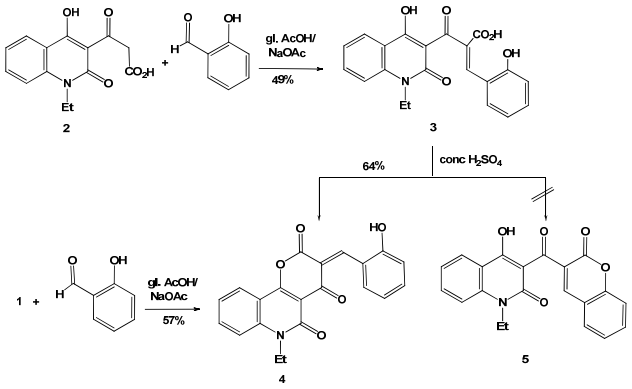
mL) and freshly fused sodium acetate (0.2 g), was heated at reflux for 3h (Scheme 2). The yellow crystals obtained after cooling were filtered and recrystallized from acetic acid to give **3** as yellow crystals. M.p.: 256 °C. Yield: 0.37 g, 49%. IR (KBr, cm^{-1}): 3429 (OH), 3045 ($CH_{arom.}$), 2975, 2890 (CH_3, CH_2), 1724 ($C=O_{carboxy}$), 1642 ($C=O_{quinolinone}$), 1603 ($C=O_{ketone}$). ^1H NMR (DMSO-d_6, δ): 1.14 (t, 3H, *J*=6.8 Hz, CH_3), 4.17 (q, 2H, *J*=6.8 Hz, CH_2), 5.70 (s, 1H, $CH_{methine}$), 7.36–7.88 (m, 6H, Ar-H), 8.15-8.18 (m, 2H, Ar-H), 11.72 (br, 1H exchangeable with D_2O, $OH_{salicylaldehyde}$), 14.69 (br, 2H exchangeable with D_2O, $OH_{quinoline}$ and $OH_{carboxy}$). Anal. Calcd for $C_{21}H_{17}NO_6$ (379.36): C, 66.49; H, 4.52; N, 3.69%. Found: C, 66.42; H, 4.36; N, 3.46%.



Scheme 1



Scheme 2

2.4. 6-Ethyl-3-(2-hydroxybenzylidene)-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H) trione (4)

2.4.1. Method A

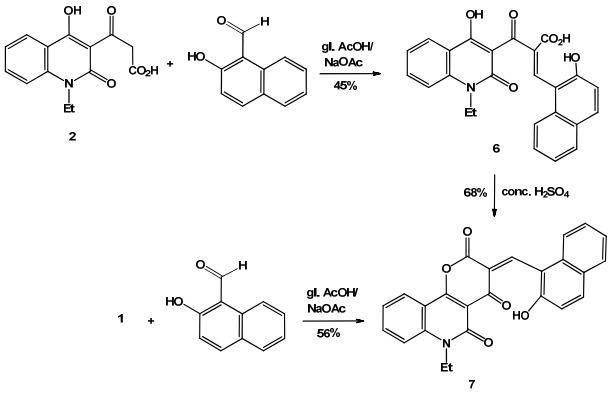
Compound **3** (0.379 g, 1 mmol) in concentrated H_2SO_4 (5 mL) was heated on a water bath for 2h. After cooling, the reaction mixture was poured onto ice/water, the precipitate so formed was filtered, washed several times with H_2O and crystallized from DMF to give **4** as yellow crystals. M.p.: 240-241 °C. Yield: 0.23 g, 64% (Scheme 2).

2.4.2. Method B

A mixture of compound **1** (0.514 g, 2 mmol) and salicylaldehyde (0.21 mL, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated at reflux for 3h, the yellow crystals obtained after cooling were filtered and recrystallized from DMF to give **4** as yellow crystals (Scheme 2). M.p.: 241 °C. Yield: 0.41 g, 57%. IR (KBr, cm^{-1}): 3430 (OH), 3044 ($CH_{arom.}$), 2976, 2920 (CH_3, CH_2), 1725 (OC=O), 1642 ($C=O_{quinolinone}$), 1611 ($C=O_{ketone}$). ^1H NMR (DMSO-d_6, δ): 1.13 (t, 3H, *J*= 6.9 Hz, CH_3), 4.13 (q, 2H, *J*= 6.9 Hz, CH_2), 7.29-7.43 (m, 4H, Ar-H), 7.54 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.69 (t, 1H, *J*= 7.5 Hz, Ar-H), 7.78-7.82 (m, 2H, Ar-H), 8.13 (s, 1H, $CH_{methine}$). ^{13}C NMR (DMSO-d_6, δ): 12.4 (CH_3), 36.2 (CH_2), 106.5 (C_{4a}), 114.8 (C_7), 116.1 ($C_{3'}$), 118.3 ($C_{5'}$), 120.5 (C_{10a}), 122.1 (C_9), 125.6 ($C_{4'}$), 125.3 ($C_{6'}$), 129.1 (C_8), 130.1 (C_{10}), 132.5 (C_3), 135.2 ($C_{1'}$), 139.0 (C_{6a}), 140.4 ($CH_{methine}$), 153.3 (C_{10b} as C-O), 157.4 ($C_{2'}$), 168.9 (C_5 as C=O), 173.3 (C_2 as C=O), 201.5 (C_4 as C=O). M/z (relative intensity): 362 (M^+ +1, 28), 361 (M^+, 100), 332 (22), 304 (11), 288 (67), 261 (11), 188 (25), 160 (8), 132 (10), 118 (6), 101 (3), 77 (2). Anal. Calcd for $C_{21}H_{15}NO_5$ (361.35): C, 69.80; H, 4.18; N, 3.88%. Found: C, 69.43; H, 4.26; N, 3.79%.

2.5. 2-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)carbonyl]-3-(1-hydroxy naphthalen-2-yl)-prop-2-enoic acid (6)

A mixture of *β*-ketoacid **2** (0.55 g, 2 mmol) and 2-hydroxy-1-naphthaldehyde (0.344 g, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4h (Scheme 3). The yellow crystals obtained after cooling were filtered and recrystallized from acetic acid to give **6** as yellow crystals. M.p.: 280 °C. Yield: 0.39 g, 45%. IR (KBr, cm^{-1}): 3496, 3350, 3200 (3OH), 3063 ($CH_{arom.}$), 2979, 2885 (CH_3, CH_2), 1719 ($C=O_{carboxy}$), 1617 ($C=O_{quinolinone}$ and $C=O_{ketone}$). ^1H NMR (DMSO-d_6, δ): 1.13 (t, 3H, *J*=7.8 Hz, CH_3), 4.14 (q, 2H, *J*=7.8 Hz, CH_2), 5.60 (s, 1H, $CH_{methine}$), 7.33-8.10 (m, 8H, Ar-H), 8.58-8.91 (m, 2H, $CH_{methine}$), 10.81 (br, 1H exchangeable with D_2O, $OH_{naphthalene}$), 13.50 (br, 2H exchangeable with D_2O, $OH_{quinolinone}$ and $OH_{carboxy}$). Anal. Calcd for $C_{25}H_{19}NO_6$ (429.43): C, 69.92; H, 4.46; N, 3.26%. Found: C, 69.60; H, 4.60; N, 3.08%.



Scheme 3

2.6. 6-Ethyl-3-[(2-hydroxynaphthalen-1-yl)methylidene)]-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)trione (7)

2.6.1. Method A

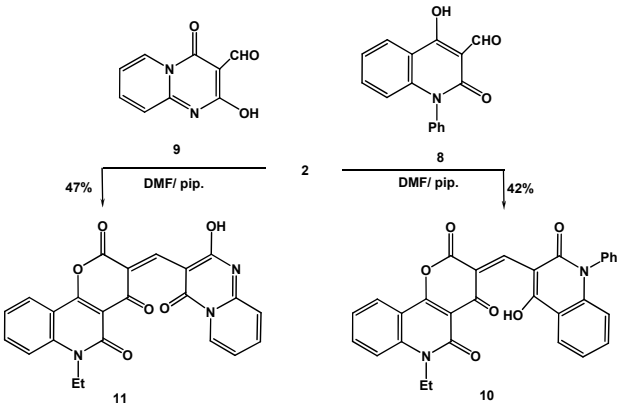
Compound **6** (0.429 g, 1 mmol) in concentrated H_2SO_4 (5 mL) was heated on a water bath for 2h. After cooling the reaction mixture was poured onto ice/water, the precipitate so formed was filtered, washed several times with H_2O and crystallized from acetic acid to give **7** as yellow crystals. M.p.: 177 °C. Yield: 0.28 g, 68% (Scheme 3).

2.6.2. Method B

A mixture of compound **1** (0.514 g, 2 mmol) and 2-hydroxy-1-naphthaldehyde (0.34 g, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4 h. The yellow crystals obtained after cooling were filtered and recrystallized from DMF to give **7** as white crystals (Scheme 3). M.p.: 177 °C. Yield: 0.46 g, 56%. IR (KBr, cm^{-1}): 3432 (OH), 3055 ($CH_{arom.}$), 2976, 2927 (CH_3, CH_2), 1715 (OC=O), 1673 ($C=O_{quinolinone}$), 1619 ($C=O_{ketone}$). ^1H NMR (DMSO-d_6, δ): 1.24 (t, 3H, *J*=7.4 Hz, CH_3), 4.36 (q, 2H, *J*=7.4 Hz, CH_2), 7.48-7.99 (m, 10H, Ar-H), 8.23 (s, 1H, $CH_{methine}$), 14.45 (br, 1H exchangeable with D_2O, $OH_{naphthalene}$). Anal. Calcd ($C_{25}H_{17}NO_5$ (411.41): C, 72.99; H, 4.16; N, 3.40%. Found: C, 72.52; H, 4.08; N, 3.28%.

2.7. 6-Ethyl-3-(4-hydroxy-1-phenyl-2-oxo-1,2-dihydro-quinolin-3-yl)methylidene)2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)trione (10)

A mixture of *β*-ketoacid **2** (0.275 g, 1 mmol) and 4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxaldehyde (**8**) (0.265 g, 1 mmol) in DMF (5 mL) containing few drops of piperidine was heated at reflux for 2h. The solid deposited after cooling was filtered and recrystallized from DMF to give **10** as yellow crystals (Scheme 4). M.p.: 265 ºC. Yield: 0.21 g, 42%. IR (KBr, cm^{-1}): 3445 (OH), 3058 ($CH_{arom.}$), 2934, 2859 (CH_2, CH_3), 1746 (OC=O), 1661 (2C=$O_{quinolinone}$), 1636 (C=O_{ketone}). ^{1}H NMR (DMSO-d_6, δ): 1.22 (t, 3H, CH_3), 4.34 (q, 2H, CH_2), 6.61-6.64 (m, 2H, Ar-H), 7.35-7.45 (m, 4H, Ar-H), 7.59-7.65 (m, 5H, Ar-H), 8.05 (s, 1H, $CH_{methine}$), 8.09-8.14 (m, 2H, Ar-H). ^{13}C NMR (DMSO-d_6, δ): 14.2 (CH_3), 42.3 (CH_2), 110.2, 113.7, 115.1, 115.6, 115.7, 116.2, 118.6, 118.8, 120.5, 120.9, 127.0, 129.6, 130.2, 130.3, 130.6, 131.7, 136.0, 139.5, 143.5 ($CH_{methine}$), 153.4, 154.7, 163.0 (C_2 as C=O), 165.3 (C_5 as C=O), 167.9 (C_2 as C=O), 194.5 (C_4 as C=O). Anal. Calcd for $C_{30}H_{20}N_2O_6$ (504.49): C, 71.36; H, 3.96, N, 5.55%. Found: C, 71.32; H, 3.87; N, 5.90%.



Scheme 4

2.8. 6-Ethyl-3-[(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)methylidene]-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (11)

A mixture of *β*-ketoacid **2** (0.275 g, 1 mmol) and 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxaldehyde (**9**) (0.19 g, 1 mmol) in DMF (5 mL) containing few drops of piperidine was heated at reflux for 2h. The solid deposited after cooling was filtered and recrystallized from DMF to give **11** as orange crystals (Scheme 4). M.p.: 215 ºC. Yield: 0.20 g, 47%. IR (KBr, cm^{-1}): 3407 (OH), 3060 ($CH_{arom.}$), 2978, 2927 (CH_2, CH_3), 1732 (OC=O), 1671 (2C=O), 1623 (C=O_{ketone}). ^{1}H NMR (DMSO-d_6, δ): 1.29 (t, 3H, *J*=7 Hz, CH_3), 4.39 (q, 2H, *J*=7 Hz, CH_2), 7.30-7.92 (m, 7H, Ar-H), 8.02 (s, 1H, $CH_{methine}$), 8.08 (d, 1H, *J*=7.2 Hz, Ar-H), 14.14 (bs, 1H exchangeable with D_2O, OH). Anal. Calcd for $C_{23}H_{15}N_3O_6$ (429.38): C, 64.33; H, 3.51, N, 9.79%. Found: C, 64.33; H, 3.70; N, 9.71%.

2.9. 3-(2-Amino-4-oxo-4H-chromen-3-yl)methylidene)-6-ethyl-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (14a,b)

2.9.1. Method A

A mixture of *β*-ketoacid **2** (0.55 g, 2 mmol) and 2-amino-3-formyl chromones **12a, b** (2 mmol) in DMF (10 mL) containing few drops of piperidine was heated at reflux for 2h. The solid deposited after cooling was filtered and recrystallized from DMF to give **14a, b** as yellow crystals (Scheme 5).

2.9.2. Method B

A mixture of compound **1** (0.514 g, 2 mmol) and 2-amino-3-formylchromones **12a, b** (2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated at reflux for 2h. The solid deposited after cooling was filtered and recrystallized from DMF to give **14a, b** as yellow crystals (Scheme 5).

2.9.3. Method C

A mixture of β-ketoacid **2** (0.55 g, 2 mmol) and chromone-3-carbonitriles **16a, b** (2 mmol) in DMF (10 mL) containing few drops of piperidine was heated at reflux for 1h. The solid deposited after cooling was filtered and recrystallized from DMF to give **14a, b** as yellow crystals (Scheme 6).

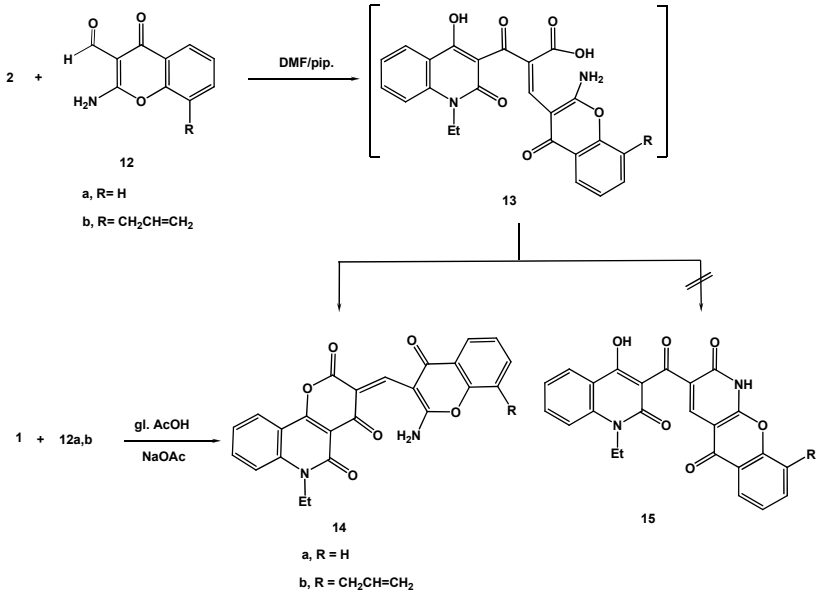
For compound **14a**: M.p.: 277 ºC. Yield: 48-55%. IR (KBr, cm^{-1}): 3437 (NH_2), 3068 ($CH_{arom.}$), 2977, 2933, 2867 (CH_3, CH_2), 1732 (OC=O), 1657 (C=$O_{γ\text{-}pyrone}$ C=$O_{quinolinone}$ and C=O_{ketone}). ^{1}H NMR (DMSO-d_6, δ): 1.29 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 7.22-7.84 (m, 8H, Ar-H), 8.02 (s, 1H, $CH_{methine}$), 8.40 (br, 1H exchangeable with D_2O, 1H of NH_2), 8.99 (br, 1H exchangeable with D_2O, 1H of NH_2). M/z (relative intensity): 428 (M^+, 0.5), 342 (87), 314 (100), 297 (42), 286 (23), 268 (3), 257 (6), 241 (6), 229 (9), 214 (8), 189 (4), 171 (4), 157 (2). Anal.Caled for $C_{24}H_{16}N_2O_6$ (428.39): C, 67.29; H, 3.76; N, 6.54%. Found: C, 67.24; H, 3.65; N, 6.20%.

For compound **14b**: M.p.: 213 ºC. Yield: 43-51%. IR (KBr, cm^{-1}): 3438 (NH_2), 3076 ($CH_{arom.}$), 2972, 2929 (CH_2, CH_3), 1736 (OC=O), 1661 (C=$O_{γ\text{-}pyrone}$, C=$O_{quinoline}$ and C=O_{ketone}). ^{1}H NMR (DMSO-d_6, δ): 1.31 (t, 3H, CH_3), 3.76 (br, 2H, CH_2), 4.37 (q, 2H, CH_2), 5.18 (m, 2H, CH=CH_2), 6.15 (m, 1H, CH=CH_2), 7.25-7.94 (m, 7H, Ar-H), 8.04 (s, 1H, $CH_{methine}$), 8.71 (br, 1H exchangeable with D_2O, 1H of NH_2), 9.92 (br, 1H exchangeable with D_2O 1H of NH_2). Anal. Calcd for $C_{27}H_{20}N_2O_6$ (468.46). C. 69.22; H, 4.30, N, 5.98%. Found: C, 69.02; H, 4.07; N, 5.72%.

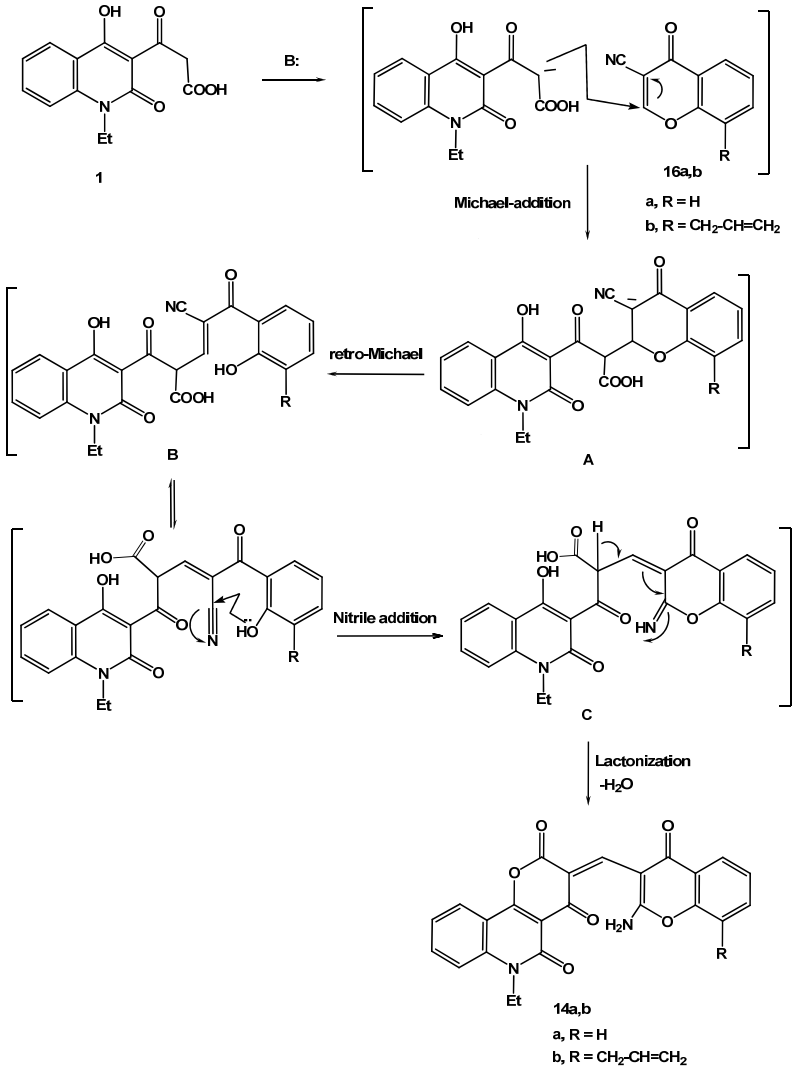
3. Results and Discussion

In the course of the present work, we found, warming pyranoquinolinone (**1**) in sodium hydroxide solution (1N) at 40-50 ºC for 30 min. afforded the novel 3-(1-ethy1-4-hydroxy-2-oxo-2(1*H*)-quinolin-3-yl)-3-oxo-propanoic acid (**2**) in 76% yield (Scheme 1). Structure of compound **2** was confirmed from its correct elemental analysis and spectral data. The ^{1}H NMR spectrum showed a characteristic singlet signal at δ 5.56 ppm attributed to the active methylene protons, in addition to two exchangeable signals at δ 12.02 and 13.41 ppm assigned to 2OH protons. The mass spectrum of compound **2** did not show the molecular ion peak at m/z 275 but showed a peak at m/z 257 which was in agreement with its molecular mass after loss of one molecule of water, and the base peak at m/z 229.

Some new quinolinone derivatives were prepared from the reaction of *β*-ketoacid **2** with different *ortho*-hydroxyaldehydes and *ortho*-aminoaldehydes. Thus, condensation of **2** with salicylaldehyde in glacial acetic acid containing freshly fused sodium acetate gave the Knoevenagel condensation product **3** (Scheme 2). The ^{1}H NMR spectrum of compound **3** revealed the presence of two exchangeable signals at *δ* 11.71 ($OH_{salicylaldehyde}$) and 14.69 ppm ($OH_{quinolinone}$ and $OH_{carboxy}$). Compound **3** can undergo intramolecular cyclization in the presence of concentrated H_2SO_4 leading to either pyranoquinoline derivative **4** or coumarine derivative **5** (Scheme 2). The product obtained from this reaction was found to be identical (the same mp, mixed mp and identical spectra) with the product obtained from the reaction of pyranoquinoline **1** and salicylaldehyde, in glacial acetic acid and freshly fused sodium acetate. Therefore, cyclization of compound **3** in concentrated



Scheme 5



Scheme 6

H_2SO_4 yielded 6-ethyl-3-(2-hydroxybenzylidene)pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,6*H*)-trione (**4**) not the coumarine derivative **5**. The reaction of pyranoquinoline **1** with salicylaldehyde proceeds through the tautomeric 1,3-dione form, which in turn possesses an active methylene group. The IR spectrum of compound **4** showed characteristic absorption bands at 3430 (OH), 1725 (O-C=O) and 1642 cm^{-1} (C=O). The methine proton observed at δ 8.13 ppm in the ^{1}H NMR spectrum, while the methine carbon appeared at δ 140.4 ppm in the ^{13}CNMR spectrum. The structure of compound **4** was further deduced from its mass spectrum which revealed the molecular ion peak at m/z 361 as the base peak, which is coincident with the formula weight (361.35) and support the identity of the structure.

Similarly, condensation of *β*-ketoacid **2** with 2-hydroxy-1-naphthaldehyde, in glacial acetic acid and freshly fused sodium acetate, afforded the Knoevenagel condensation product **6** which underwent intramolecular cyclization in the presence of concentrated H_2SO_4 to yield 6-ethyl-3-(2-hydroxy-1-naphthylidene)pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,6*H*)-trione(**7**). Compound **7** was also obtained from the condensation of 4-hydroxypyranoquinoline derivative **1** with 2-hydroxy-1-naphthaldehyde (Scheme 3).

Interestingly, condensation of *β*-ketoacid **2** with 4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxaldehyde (**8**) [19] and 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxaldehyde (**9**) [20] in boiling DMF, containing few drops of piperidine, furnished directly the cyclized products, 6-ethyl-3-[(4-hydroxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)met hyldene-2*H*-pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,6*H*)-trione (**10**) and 6-ethyl-3-[(2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methylidene]-2*H*-pyrano[3,2-*c*]quinoline-2,4,5-(3*H*,6*H*)-tri one (**11**), respectively, in one step reactions. Under these reaction conditions the Knoevenagel condensation intermediates were not isolated, but underwent intramolecular nucleophilic lactonization to form the cyclized products **10** and **11** (Scheme 4).

On the other hand, when β-ketoacid **2** was subjected to react with 2-amino chromone-3-carboxaldehyde (**12a**) [21] and its 8-allyl analog **12b**, [22] in boiling DMF containing few drops of piperidine as a catalyst, pyranoquinoline derivatives **14a, b** or chromenopyridine derivatives **15a, b** were expected as products for this reaction (Scheme 5). Herein again, the reaction proceeds initially *via* Knoevenagel condensation to produce the intermediates **13a** and **13b**, respectively. These intermediates can undergo intramolecular nucleophilic lactonization forming pyranoquinoline derivatives **14a, b** or lactimization forming chromenopyridine derivatives **15a, b**. The elemental and mass analyses of the products are not differential because both structures are isomers. The ^{1}H NMR spectra were used to distinguish the structure of the products. The signals assigned to the OH and NH protons of compounds **15a, b** were not observed in the spectra, and therefore structures **15a, b** were excluded. The spectra of compounds **14a, b** showed characteristic exchangeable signals attributed to the NH_2 protons. Compounds **14a** and **14b** were also obtained from the reaction of pyranoquinoline **1** with 2-aminochromone-3-carboxaldehydes (**12a, b**) in glacial acetic acid and freshly fused sodium acetate.

In continuation to our previous work on the chemistry of chromone-3-carbonitrile [23], we found that 2-amino-3-formylchromone is chemically equivalent to chromone-3-carbonitrile under certain nucleophilic conditions. Thus, treating β-ketoacid **2** with chromone-3-carbonitriles (**16a, b**) [21,22] in boiling DMF containing few drops of piperidine afforded compounds **14a, b**. Formation of compounds **14a, b** from carbonitriles **16a, b** was accomplished *via* a tandem cyclization reaction through *Michael* addition of the active methylene group in compound **2** to the γ-pyrone moiety of carbonitriles **16a, b** producing intermediates **A** (non-isolable). The base-mediated retro-*Michael* reaction of **A** gave the open chain intermediates **B** (non-isolable), the attack of hydroxyl group onto the nitrile function gave intermediates **C** (non-isolable) which underwent lactonization leading to **14a, b**. The transformation of **16** into **14** can be regarded as a domino "*Michael* / retro-*Michael* / nitrile-addition / lactonization" as shown in Scheme 6 [24].

4. Conclusion

We have developed a new and convenient method for the synthesis of novel pyrano[3,2-*c*]quinolinone derivatives *via* condensation reactions of 3-(1-ethyl-4-hydroxy-2-oxo-2(1*H*)-quinolin-3-yl)-3-oxopropanoic acid with some *ortho*-hydroxyaldehydes and *ortho*-aminoaldehydes.

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