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Synthesis and antimicrobial activity of some novel 4-hydroxyquinolin-2(1*H*)-ones and pyrano[3,2-*c*] quinolinones from 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid

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Chlorination, bromination, and condensation reactions of 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**3**) were studied. Some novel 4-hydroxyquinolin-2(1*H*)-ones and pyrano[3,2-*c*]quinolin-2(1*H*)-ones were also prepared. The structures of the novel compounds were established by elemental analyses and spectral data. All the products were also screened in vitro for their antimicrobial activity.

Key Words: *β*-Ketoacid, 4-hydroxyquinolin-2(1*H*)-one, pyrano[3,2-*c*]quinolinone, condensation reactions

Introduction

Pyranoquinolinones constitute the parent ring structure of pyranoquinoline alkaloids, which occur in the plant family Rutaceae. These pyranoquinoline alkaloids have gained considerable importance due to their pharmaceutical activities like anticoagulant,[1] coronary constricting,[2] and antifungal.[3] Pyrano[3,2-*c*]quinolinones were found to be active against certain immuno-reaction diseases, in particular against immediate hypersensitivity reactions (anaphylaxis).[4] In turn, these pyranoquinolinones were used to obtain 4-hydroxyquinolin-2(1*H*)-ones

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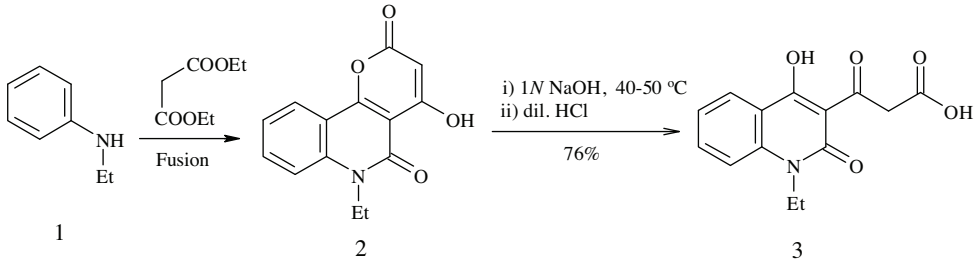
and 3-acetyl-4-hydroxyquinolin-2(1*H*)-one derivatives.[5,6] Moreover, a broad number of important pharmacological activities have been associated with 3-substituted-4-hydroxyquinolin-2(1*H*)-ones.[7–9] Many derivatives of this heterocyclic category are biologically active naturally occurring compounds, which were found to be useful intermediates for many medicinal products.[10,11] Heating *N*-ethylaniline with 2 equivalent diethylmalonate gave 4-hydroxypyrano[3,2-*c*]quinolin-2(1*H*)-one **2** in a one-pot double cyclocondensation process.[12,13] In our previous work, 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxo-propanoic acid (**3**) was prepared (Scheme 1) and its chemical reactivity was studied towards some *o*-hydroxyaldehydes and *o*-aminoaldehydes.[14] In the present work, the chemical reactivity of *β*-ketoacid **3** was studied towards some electrophilic and condensation reactions, aiming to obtain a new multi-functionalized quinolinone and pyrano[3,2-c]quinolinone derivatives and the antimicrobial activity of the synthesized products was evaluated.



Scheme 1. Formation of *β*-ketoacid **3**.

Experimental

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. ^{1}H-NMR spectra were measured on a Gemini-200 spectrometer (200 MHz), Mercury-300BB (300 MHz), and/or Jeol Eca-500 MHz using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using a GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

3-(1-Ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxo-propanoic acid (3)

This compound was prepared according to our published method.[14]

3-(2,2-Dichloroacetyl)-1-ethyl-4-hydroxyquinolin-2(1H)-one (5)

To a suspension of *β*-ketoacid **3** (0.55 g, 2 mmol) in 1,4-dioxane (30 mL), sulfuryl chloride (2 mmol) was added portionwise, while the temperature was not allowed to rise above 40 °C. Then the reaction mixture was stirred for 1 h at room temperature and poured on ice-H_2O (200 mL). The formed precipitate was collected by filtration and crystallized from ethanol to give compound **5** as yellow crystals, yield (0.39 g, 59%), mp 185 °C (lit. 184-186 °C).[15,16] IR (KBr, cm^{-1}): 3390 (OH), 3071 ($CH_{arom.}$), 2935, 2895 ($CH_{aliphatic}$), 1656 (2C=O), 1604 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.17 (t, 3H, J = 6.5 Hz, CH_2CH_3), 4.23 (q, 2H, J = 6.5 Hz,

CH_2CH_3), 7.35 (t, 1H, J = 7.6 Hz, H-6), 7.62 (d, 1H, J = 7.6 Hz, H-8), 7.83 (t, 1H, J = 7.6 Hz, H-7), 7.87 (s, 1H, $CHCl_2$), 8.14 (d, 1H, J = 7.6 Hz, H-5).

3-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,2-dibromo-3-oxopropanoic acid (6)

A solution of bromine (2 mmol) in acetic acid (10 mL) was added dropwise to a solution of β-ketoacid **3** (0.55 g, 2 mmol) in acetic acid (10 mL). The reaction mixture was heated under reflux for 2 h. The solid obtained after cooling was filtered and recrystallized from ethanol to give **6** as yellow crystals, yield (0.37 g, 43%), mp 240 °C. IR (KBr, cm^{-1}): 3414 (2OH), 3084 ($CH_{arom.}$), 2980, 2933, 2867 ($CH_{aliphatic}$), 1719 ($C{=}O_{acid}$), 1672 ($C{=}O_{quinoline}$), 1617 ($C{=}O_{ketone}$). ^{1}H-NMR (DMSO-d_6, δ): 1.27 (t, 3H, J = 7.2 Hz, CH_2CH_3), 4.34 (q, 2H, J = 7.2 Hz, CH_2CH_3), 7.50 (t, 1H, J= 6.4 Hz, H-6), 7.82-7.88 (m, 2H, H-7 and H-8), 8.11 (d, 1H, J = 7.8 Hz, H-5), 14.42 (br, 2H, 2OH exchangeable with D_2O). Anal. Calcd for $C_{14}H_{11}Br_2NO_5$ (433.06): C, 38.83; H, 2.56; N, 3.23; Br, 36.90%. Found C, 38.52; H, 2.65; N, 3.35; Br, 36.55%.

3,3-Dibromo-6-ethylpyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (8)

Method A

Compound **6** (0.87 g, 2 mmol) in concentrated H_2SO_4 (5 mL) was stirred at room temperature for 1 h. The dark reddish solution was poured onto ice/water, and the precipitate so formed was filtered, washed several times with water, and crystallized from ethanol to give **8** as yellow crystals, yield (0.46 g, 55%), mp 205 °C.

Method B

A solution of bromine (2 mmol) in acetic acid (10 mL) was added dropwise to a solution of compound **2** (0.51 g, 2 mmol) in acetic acid (10 mL). The reaction mixture was heated under reflux for 2 h. The solid obtained after cooling was filtered and recrystallized from ethanol to give **8** as yellow crystals, yield (0.34 g, 62%), mp 204-205 °C. IR (KBr, cm^{-1}): 3074 ($CH_{arom.}$), 2980, 2934 ($CH_{aliphatic}$), 1730 (OC=O), 1669 (2C= O), 1612 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.36 (t, 3H, CH_2CH_3), 4.44 (q, 2H, CH_2CH_3), 7.58 (br, 1H, Ar-H), 7.93 (br, 2H, Ar-H), 8.16 (br, 1H, Ar-H). M/z (relative intensity): 335 [M-Br; 43], 306 (13), 228 (9), 188 (5), 172 (100), 144 (32), 119 (21), 114 (23), 101 (33), 90 (31), 77 (77), 64 (39). Anal. Calcd for $C_{14}H_9Br_2NO_4$ (415.04): C, 40.52; H, 2.15; Br, 38.50; N, 3.37%. Found C, 40.28; H, 2.03; Br, 38.01; N, 3.29%.

3-(2,2-Dibromoacetyl)-1-ethyl-4-hydroxyquinolin-2(1H)-one (9)

Compound **8** (0.83 g, 2 mmol) was dissolved in 2 M aqueous sodium hydroxide solution (50 mL) and heated under reflux for 3 h. The solution obtained after cooling was acidified with conc. hydrochloric acid. The precipitated so formed was filtered, washed with water, air dried, and crystallized from AcOH to give **9** as white crystals, yield (0.48 g, 62%), mp 213 °C. IR (KBr, cm^{-1}): 3416 (OH), 3068 ($CH_{arom.}$), 2922, 2870 ($CH_{aliphatic}$), 1664 (2C= O), 1605 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.25 (t, 3H, J = 6.9 Hz, CH_2CH_3), 4.44 (q, 2H, J = 6.9 Hz, CH_2CH_3), 6.40 (s, 1H, $CHBr_2$), 7.42 (t, 1H, J = 7.6 Hz, H-6), 7.75-7.83 (m, 2H, H-7 and H-8), 8.11 (d, 1H, J = 8.4 Hz, H-5). M/z (relative intensity): 317 [M-70; 42], 319 (100), 321 (39), 237 (3), 224 (6), 200 (16), 159 (3), 144 (3), 117 (9), 103 (16), 90 (6). Anal. Calcd for $C_{13}H_{11}Br_2NO_3$ (389.05): C, 40.14; H, 2.85; N, 3.60; Br, 41.08%. Found C, 39.83; H, 2.69; N, 3.43; Br, 40.81%.

2-Bromo-5-ethyl-3-hydroxyfuro[3,2-c]quinolin-4(5H)-one (10)

Compound **9** (0.78 g, 2 mmol) was dissolved in DMF (10 mL) containing a few drops of triethylamine and heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was poured onto ice/water. The precipitated so formed was filtered, washed with water, air dried and crystallized from dioxane/water to give **10** as yellow crystals, yield (0.27 g, 44%), mp 266 °C. IR (KBr, cm^{-1}): 3423 (OH), 3075 ($CH_{arom.}$), 2972, 2920 ($CH_{aliphatic}$), 1672 (C= $O_{quinolinone}$), 1631 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.13 (t, 3H, J = 6.7 Hz, CH_2CH_3), 4.20 (q, 2H, J = 6.7 Hz, CH_2CH_3), 7.67 (d, 1H, H-6), 7.78–7.91 (m, 2H, H-7 and H-8), 8.11 (d, 1H, H-9). Anal. Calcd for $C_{13}H_{10}BrNO_3$ (308.13): C, 50.67; H, 3.27; N, 4.55; Br, 25.93%. Found C, 50.90; H, 3.30; N, 4.60; Br, 25.80%.

6-Ethyl-3-[(6-methyl-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3H)-yl)imino]pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (11)

A mixture of compound **8** (0.41 g, 1 mmol) and 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one (0.16 g, 1 mmol) in DMF (5 mL) containing a few drops of piperidine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from DMF/EtOH to give **11** as yellow crystals, yield (0.25 g, 61%), mp 178 °C. IR (KBr, cm^{-1}): 3222 (NH), 3085 ($CH_{arom.}$), 2978, 2920 ($CH_{aliphatic}$), 1728 (OC=O), 1672 (3C=O), 1618 (C=N). ^{1}H-NMR (DMSO-d_6, δ): 1.24 (t, 3H, J = 6.9 Hz, CH_2CH_3), 2.67 (s, 3H, $CH_{3\,triazine}$), 4.33 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.82 (t, 1H, H-9), 7.85-8.01 (m, 2H, H-7 and H-8), 8.09 (d, 1H, H-10), 13.43 (bs, 1H, NH exchangeable with D_2O). Anal. Calcd for $C_{18}H_{13}N_5O_5S$ (411.3): C, 52.55; H, 3.19; N, 17.02; S, 7.79%. Found C, 52.31; H, 3.02; N, 17.11; S, 7.67%.

2-(6-Ethyl-2,4,5-trioxo-5,6-dihydro-4H-pyrano[3,2-c]quinolin-3-ylidene)-malononitrile (12)

A mixture of compound **8** (0.41 g, 1 mmol) and malononitrile (0.07 g, 1 mmol) in DMF (5 mL) containing a few drops of piperidine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from methanol to give **12** as yellow crystals, yield (0.20 g, 63%), mp 236 °C. IR (KBr, cm^{-1}): 3079 ($CH_{arom.}$), 2982, 2937, 2875 ($CH_{aliphatic}$), 2207 (2C=N), 1737 (OC=O), 1672 (2C=O), 1614 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.21 (t, 3H, J = 7.2 Hz, CH_2CH_3), 4.24 (q, 2H, J = 6.8 Hz, CH_2CH_3), 7.32 (t, 1H, J = 7.2 Hz, H-9), 7.58 (d, 1H, J = 8.0 Hz, H-7), 7.81 (t, 1H, J= 7.2 Hz, H-8), 8.11 (d, 1H, J = 8.0 Hz, H-10). Anal. Calcd for $C_{17}H_9N_3O_4$ (319.28): C, 63.95; H, 2.84; N, 13.16%. Found C, 63.76; H, 2.63; N, 13.02%

6-Ethyl-3,3-bis-phenylsulfanyl-6H-pyrano[3,2-c]quinoline-2,4,5-trione (13)

A mixture of compound **8** (0.41 g, 1 mmol) and thiophenol (0.40 mL, 2 mmol) in DMF (5 mL) containing a few drops of piperidine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from DMF to give **13** as yellow crystals, yield (0.26 g, 55%), mp 155 °C. IR (KBr, cm^{-1}): 3063 ($CH_{arom.}$), 2979, 2932, 2868 ($CH_{aliphatic}$), 1730 (OC=O), 1670 (2C=O), 1610 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.13 (t, 3H, CH_2CH_3), 4.28 (q, 2H, CH_2CH_3), 7.16-7.99 (m, 13H, Ar-H), 8.12 (d, 1H, H-10). M/z (relative intensity): 472 [M-1; 5], 255 (26), 239 (100), 228 (6), 171 (14), 144 (4), 120 (6), 105 (5), 93 (7), 78 (20). Anal. Calcd for $C_{26}H_{19}NO_4S_2$ (473.57): C, 65.94; H, 4.04; N, 2.96; S, 13.54%. Found C, 65.61; H, 3.64; N, 2.68; S, 13.37%.

6-Ethyl-1-(methylsulfanyl)-3,5,12-trioxo-4,5,6,12-tetrahydro-3H-pyrido [2‘,3‘:4,5] pyrano[3,2-c]quinoline-2-carbonitrile (14)

A mixture of β-ketoacid **3** (0.55 g, 2 mmol) and *bis*(methylthio)methylene-malononitrile and/or *bis*(methylthio) methylene-cyanoacetamide (2 mmol) in DMF (10 mL) containing a few drops of DBU was heated under reflux for 6 h. The solid obtained after cooling was filtered, washed with methanol (10 mL), and crystallized from DMF/H_2O to give **14** as yellow crystals, mp 201 °C. IR (KBr, cm^{-1}): 3443 (NH), 3083 ($CH_{arom.}$), 2943, 2864 ($CH_{aliphatic}$), 2196 (C≡N), 1743 (OC=O), 1673 (C=$O_{quinolinone}$), 1642 (C=$O_{pyridone}$). ^{1}H-NMR (DMSO-d_6, δ): 1.24 (t, 3H, J = 6.4 Hz, CH_2CH_3), 3.71 (s, 3H, SCH_3), 4.32 (q, 2H, J = 6.4 Hz, CH_2CH_3), 7.31 (t, 1H, H-9), 7.57 (d, 1H, H-7). 7.82–7.89 (m, 1H, H-8), 8.14-8.16 (m, 1H, H-10), 13.59 (b, 1H, NH exchangeable with D_2O). M/z (relative intensity): 379 (37), 278 (100), 326 (20), 311 (61), 297 (17), 195 (35), 280 (16), 252 (13), 237 (4), 194 (12), 150 (24), 136 (25), 111 (35), 94 (23), 59 (14). Anal. Calcd for $C_{19}H_{13}N_3O_4S$ (379.40): C, 60.15; H, 3.45; N, 11.08; S, 8.40%. Found C, 60.32; H, 3.53; N, 11.20, S, 8.37%.

2-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)carbonyl]-3-(1H-indol-3-yl)prop-2-enoic acid (17)

A mixture of compound **3** (0.55 g, 2 mmol) and 3-formylindol (**15**) (0.30 g, 2 mmol), in glacial acetic acid (10 mL) containing freshly fused sodium acetate (0.2 g), was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto ice/water, and the solid deposited was filtered and crystallized from AcOH/H_2O to give **17** as pale brown crystals, yield (0.43 g, 54%), mp 180-181 °C. IR (KBr, cm^{-1}): 3400 (2OH), 3166 (NH), 3095 ($CH_{arom.}$), 2981, 2929, 2877 ($CH_{aliphatic}$), 1738 (C=O_{acid}), 1673 (C=$O_{quinolinone}$), 1622 (C=O_{ketone}). ^{1}H-NMR (DMSO-d_6, δ): 1.27 (t, 3H, CH_2CH_3), 4.38 (q, 2H, CH_2CH_3), 5.61 (s, 1H, methine proton), 7.23-8.28 (m, 9H, Ar-H), 9.93 (br, 1H, NH exchangeable with D_2O), 12.14 (br, 1H, OH_{acid} exchangeable with D_2O), 13.80 (br, 1H, $OH_{quinolinone}$ exchangeable with D_2O). Anal. Calcd for $C_{23}H_{18}N_2O_5$ (402.41): C, 68.65; H, 4.51; N, 6.96%. Found C, 68.89; H, 4.18; N, 6.84%.

2-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)carbonyl]-3-(4-oxo-4H-chromen-3-yl)-prop-2-enoic acid (18)

A mixture of β-ketoacid **3** (0.55 g, 2 mmol) and 3-formylchromone (**16**) (0.35 g, 2 mmol) in glacial acetic acid (10 mL) containing freshly fused sodium acetate (0.2 g) was heated under reflux for 4 h. The solid obtained after cooling was filtered and recrystallized from acetic acid to give **18** as yellow crystals, yield (0.58 g, 67%), mp 252-253 °C. IR (KBr, cm^{-1}): 3456 (2OH), 3081 ($CH_{arom.}$), 2979, 2932 ($CH_{aliphatic}$), 1778 (C=O_{acid}), 1672 (C=$O_{quinolinone}$ and C=$O_{chromone}$), 1620 (C=O_{ketone}). ^{1}H-NMR (DMSO-d_6, δ): 1.26 (t, 3H, J = 7.2 Hz, CH_2CH_3), 4.37 (q, 2H, J = 7.2 Hz, CH_2CH_3), 5.68 (s, 1H, methine proton), 7.50 (d, 1H, J = 6.0 Hz, Ar-H), 7.64 (d, 1H, J = 8.4, Ar-H), 7.75-7.85 (m, 3H, Ar-H), 8.04-8.14 (m, 3H, Ar-H), 8.93 (s, 1H, H-$2_{chromone}$), 13.90 (br, 2H, 2OH exchangeable with D_2O). Anal. Calcd for $C_{24}H_{17}NO_7$ (431.41): C, 66.82; H, 3.97; N, 3.25%. Found C, 66.87; H, 4.20; N, 3.29%.

6-Ethyl-3-(1H-indol-3-yl)methylidene)pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (19)

Method A

Compound **17** (0.80 g, 2 mmol) in concentrated sulfuric acid (5 mL) was stirred at room temperature for 1 h and left overnight. The dark brown solution was poured onto ice/water and stirred for 1 h. The solid obtained was filtered, washed with water, and crystallized from ethanol to give **19** as pale brown crystals, yield (0.54 g, 70%), mp 162 °C.

Method B

A mixture of compound **2** (0.51 g, 2 mmol) and 3-formylindol (**15**) (0.30 g, 2 mmol) in glacial acetic acid (10 mL) containing freshly fused sodium acetate (0.2 g) was heated under reflux for 2 h. The solid obtained after cooling was filtered and crystallized from ethanol to give **19** as pale brown crystals, yield (0.44 g, 57%), mp 162 °C. IR (KBr, cm^{-1}): 3224 (NH), 3083 ($CH_{arom.}$), 2983, 2920 ($CH_{aliphatic}$), 1742 (OC=O), 1664 ($C{=}O_{quinoline}$ and $C{=}O_{ketone}$). ^{1}H-NMR (DMSO-d_6, δ): 1.25 (t, 3H, J = 6.4 Hz, CH_2CH_3), 4.34 (q, 2H, J = 6.6 Hz, CH_2CH_3), 6.75-7.53 (m, 7H, Ar-H), 7.82 (s, 1H, Ar-H), 7.94 (s, 1H, methine proton), 8.10 (d, 1H, J = 8.0 Hz, H-10), 9.78 (br, IH, NH exchangeable with D_2O). Anal. Calcd for $C_{23}H_{16}N_2O_4$ (384.39): C, 71.87; H, 4.20; N, 7.29%. Found C, 71.58; H, 4.11; N, 7.21%.

6-Ethyl-3-[(4-oxo-4H-chromen-3-yl)methylidene]pyrano[3,2-c]quinoline-2,4,5 (3H,6H)trione (20)

Method A

Compound **18** (0.43 g, 1 mmol) in concentrated sulfuric acid (5 mL) was stirred at room temperature for 1 h and left overnight. The dark brown solution was poured onto ice/water and stirred for 1 h. The solid obtained was filtered, washed with water, and crystallized from n-butanol to give **20** as yellow crystals, yield (0.32 g, 78%), mp 241-242 °C.

Method B

A mixture of compound **2** (0.51 g, 2 mmol) and 3-formylchromone (**16**) (0.35 g, 2 mmol) in glacial acetic acid (10 mL) containing freshly fused sodium acetate (0.2 g) was heated under reflux for 2 h. The solid obtained after cooling was filtered and crystallized from n-butanol to give **20** as yellow crystals, yield (0.58 g, 71%), mp 241-242 °C. IR (KBr, cm^{-1}): 3088 ($CH_{arom.}$), 2978, 2939 ($CH_{aliphatic}$), 1744 (OC=O), 1661 ($C{=}O_{quinoline}$, $C{=}O_{\gamma-pyrone}$, and $C{=}O_{ketone}$). ^{1}H-NMR (DMSO-d_6, δ): 1.15 (t, 3H, J = 6.8 Hz, CH_2CH_3), 4.09 (q, 2H, J = 6.8 Hz, CH_2CH_3), 7.43-7.77 (m, 8H, Ar-H), 8.35 (s, 1H, methine proton), 8.81 (s, 1H, H-$2_{chromone}$). M/z (relative intensity): 413 (15), 386 (4), 358 (4), 330 (3), 316 (10), 288 (8), 257 (58), 229 (87), 201 (21), 171 (100), 145 (47), 132 (54), 117 (28), 92 (38), 77 (78). Anal. Calcd for $C_{24}H_{15}NO_6$ (413.39): C, 69.73; H, 3.66; N, 3.39%. Found C, 69.48; H, 3.57; N, 3.41%.

Formation of compounds 22-24: general procedure

A mixture of β-ketoacid **3** (0.55 g, 2 mmol) and some aldehyde derivatives, namely piperonal, 2-formylpyridine, and 2-chloro-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (**21**) (2 mmol), in DMF (10 mL) containing a few drops of piperidine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from the appropriate solvent to give compounds **22-24**, respectively.

3-(1,3-Benzodioxol-5-ylmethylidene)-6-ethyl-pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (22)

Crystallized from DMF/MeOH as yellow crystals, yield (0.46 g, 59%), mp 180-181 °C. IR (KBr, cm^{-1}): 3075 ($CH_{arom.}$), 2978, 2883 ($CH_{alipatic}$), 1737 (OC=O), 1673 (2C=O), 1619 (C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.25 (t, 3H, J = 6.4 Hz, CH_2CH_3), 4.35 (q, 2H, J = 6.4 Hz, CH_2CH_3), 5.96 (s, 2H, -OCH_2O-), 6.75-7.53 (m, 5H, Ar-H), 7.82 (s, 1H, Ar-H), 7.95 (s, 1H, methine proton), 8.10 (d, 1H, J = 8.0 Hz, Ar-H). Anal. Calcd for $C_{22}H_{15}NO_6$ (389.35): C, 67.86; H, 3.88; N, 3.60%. Found C, 67.65; H, 3.72; N, 3.44%.

6-Ethyl-3-(pyridin-2-ylmethylidene)pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (23)

Crystallized from DMF/H_2O as pale brown crystals, yield (0.29 g, 41%), mp 220-221 °C. IR (KBr, cm^{-1}): 3080 ($CH_{arom.}$), 2980, 2871 ($CH_{aliphatic}$), 1739 (OC=O), 1674 (2C=O), 1618 (C=N and C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.17 (t, 3H, CH_2CH_3), 4.35 (q, 2H, CH_2CH_3), 7.05-7.86 (m, 8H, Ar-H), 8.17 (s, 1H, methine proton). M/z (relative intensity): 332 [M-14; 3], 308 (5), 290 (10), 257 (78), 229 (100), 214 (7), 201 (29), 173 (23), 145 (26), 132 (14), 104 (8), 89 (8), 77 (20). Anal. Calcd for $C_{20}H_{14}N_2O_4$ (346.33): C, 69.36; H, 4.07; N, 8.09%. Found: C, 69.15; H, 3.89; N, 8.01%.

3-[(2-Chloro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl) methylidene]-6-ethylpyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (24)

Crystallized from DMF as orange crystals, yield (0.52 g, 58%), mp 239-240 °C. IR (KBr, cm^{-1}): 3074 ($CH_{arom.}$), 2971, 2931, 2864 ($CH_{aliphatic}$), 1730 (OC=O), 1652 (3C=O). ^{1}H-NMR (DMSO-d_6, δ): 1.24 (t, 3H, J= 6.8 Hz, CH_2CH_3), 4.31 (q, 2H, J = 7.0 Hz, CH_2CH_3), 7.19-7.33 (m, 3H, Ar-H), 7.39-7.66 (m, 3H, Ar-H), 7.71-8.09 (m, 3H, 2Ar-H and methine proton). M/z (relative intensity): 445 [M-2; 5], 391 (40), 254 (91), 240 (75), 229 (15), 201 (13), 161 (68), 146 (43), 144 (25), 120 (63), 117 (35), 104 (25), 92 (10), 78 (100). Anal. Calcd for $C_{23}H_{14}ClN_3O_5$ (447.82): C, 61.69; H, 3.15; N, 9.38%. Found C, 61.72; H, 3.24; N, 9.23%.

1-Ethyl-4-hydroxy-3-{5-oxo-4-[(4-oxo-4H-chromen-3-yl)methylidene]-4,5-dihydro-1H-pyrazol-3-yl} quinolin-2(1H)-one (25)

A mixture of compound **20** (0.82 g, 2 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) in ethanol containing a few drops of triethylamine (10 mL) was heated under reflux for 2 h. The solid deposited after cooling was filtered and crystallized from acetic acid to give compound **25** as yellow crystals, yield (0.41 g, 48%), mp 203-204 °C. IR (KBr, cm^{-1}): 3400, 3285, 3256 (OH, NH), 3072 ($CH_{arom.}$), 2911, 2833 ($CH_{aliphatic}$), 1678 ($C{=}O_{quinoline}$ and $C{=}O_{pyrazole}$), 1635 ($C{=}O_{\gamma-pyrone}$), 1561 (C=N and C=C). ^{1}H-NMR (DMSO-d_6, δ): 1.23 (t, 3H, J = 7.6 Hz, CH_2CH_3), 4.33 (q, 2H, CH_2CH_3), 5.52 (s, 1H, methine proton), 6.90-6.95 (m, 1H, Ar-H), 7.45-7.49 (m, 2H, Ar-H), 7.61 (d, 1H, J = 6.4 Hz, Ar-H), 7.75-7.86 (m, 2H, Ar-H), 8.03-8.10 (m, 2H, Ar-H), 8.12 (s, 1H, H-$2_{chromone}$), 13.78 (s, 2H exchangeable with D_2O, NH and OH). Anal. Calcd for $C_{24}H_{17}N_3O_5$ (427.42): C, 67.44; H, 4.01; N, 9.83%. Found C, 67.35; H, 4.05; N, 9.69%.

1-Ethyl-4-hydroxy-3-{5-[(4-oxo-4H-chromen-3-yl)methylidene]-6-oxo-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl}-quinolin-2(1H)-one (26)

A mixture of compound **20** (0.82 g, 2 mmol) and thiourea (0.15 g, 2 mmol) in ethanol containing a few drops of triethylamine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from methanol to give **26** as yellow crystals, yield (0.58 g, 62%), mp 185 °C. IR (KBr, cm^{-1}): 3425 (OH, NH), 3039 ($CH_{arom.}$), 2977, 2920 ($CH_{aliphatic}$), 1654 (3C=O), 1597 (C=N), 1219 (C=S). ^{1}H-NMR (DMSO-d_6, δ): 1.25 (t, 3H, $CH_2\,CH_3$), 4.33 (q, 2H, $CH_2\,CH_3$), 5.59 (s, 1H, methine proton), 7.10-8.26 (m, 8H, Ar-H), 8.91 (s, 1H, H-$2_{chromone}$), 10.77 (s, 1H, NH exchangeable with D_2O), 13.60 (s, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{25}H_{17}N_3O_5S$ (471.48): C, 63.69; H, 3.63; N, 8.91; S, 6.80%. Found C, 63.57; H, 3.56; N, 8.85; S, 6.72%.

4-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-5-[(4-oxo-4H-chromen-3-yl) methylidene]-6-oxo-5,6-dihydropyrimidin-2(1H)-ylidene]cyanamide (27)

A mixture of compound **20** (0.82 g, 2 mmol) and cyanoguanide (0.17 g, 2 mmol) in ethanol containing a few drops of triethylamine was heated under reflux for 4 h. The solid deposited after cooling was filtered and crystallized from ethanol to give **27** as yellow crystals, yield (0.48 g, 50%), mp 235-236 °C. IR (KBr, cm^{-1}): 3425 (OH, NH), 3030 ($CH_{arom.}$), 2976, 2928 ($CH_{aliphatic}$), 2176 (C≡N), 1627 (3C=O). ^{1}H-NMR (DMSO-d_6, δ): 1.16 (t, 3H, $CH_2\,CH_3$), 4.18 (q, 2H, $CH_2\,CH_3$), 5.83 (s, 1H, methine proton), 6.89-6.92 (m, 2H, Ar-H), 7.19-7.49 (m, 4H, Ar-H), 7.82 (t, 1H, Ar-H), 8.04-8.07 (m, 1H, Ar-H), 8.74 (s, 1H, H-$2_{chromone}$), 11.93 (s, 1H, NH exchangeable with D_2O), 13.70 (s, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{26}H_{17}N_5O_5$ (479.44); C, 65.13; H, 3.57; N, 14.61 %. Found C, 64.96; H, 4.00; N, 14.34%.

4-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-[(4-oxo-4H-chromen-3-yl) methylidene])-1,3-dihydro-2H-1,5-benzodiazepin-2-one (28)

A mixture of compound **20** (0.41 g, 1 mmol) and *o*-phenlyene diamine (0.11 g, 1 mmol) in ethanol containing a few drops of triethylamine was heated under reflux for 4 h. The solid deposited during heating was filtered and crystallized from DMF/H_2O to give **28** as yellow crystals, yield (0.27 g, 54%), mp 293-294 °C. IR (KBr, cm^{-1}): 3439 (OH, NH), 3084 ($CH_{arom.}$), 2982, 2930, 2890 ($CH_{aliphatic}$), 1640 (2C=O), 1630 (C=O), 1557 (C=N). ^{1}H-NMR (DMSO-d_6, δ): 1.13 (t, 3H, $CH_2\,CH_3$), 4.17 (q, 2H, $CH_2\,CH_3$), 5.83 (s, 1H, methine proton), 6.61 (t, 1H, Ar-H), 7.11-7.85 (m, 11H, Ar-H), 8.80 (s, 1H, H-$2_{chromone}$), 12.54 (s, 1H, NH exchangeable with D_2O), 13.60 (s, 1H, OH exchangeable with D_2O). M/z (relative intensity): 421 (31), 419 [M-3CO; 3], 403 (24), 390 (91), 375 (10), 359 (58), 331 (23), 305 (49), 290 (27), 277 (48), 214 (30), 202 (24), 188 (60), 174 (17), 161 (44), 146 (60), 130 (82), 120 (50), 104 (35), 92 (47), 77 (100), 65 (55). Anal. Calcd for $C_{30}H_{21}N_3O_5$ (503.50): C, 71.56; H, 4.20; N, 8.35%. Found C, 71.60; H, 4.08; N, 8.21%.

2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-[(4-oxo-4H-chromen-3-yl) methylidene]-9-(4-methoxyphenyl)-4,7-dioxo-4,5,6,7-tetrahydropyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile (31)

A mixture of compound **20** (0.41 g, 1 mmol) and 1,6-diamino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**29**) (0.28 g, 1 mmol) in ethanol containing a few drops of triethylamine was heated under reflux for 4 h. The solid deposited during heating was filtered and crystallized from DMF to give **31** as yellow crystals, yield (0.38 g, 67%), mp > 300 °C. IR (KBr, cm^{-1}): 3357 (OH, NH), 2973, 2930 ($CH_{aliphatic}$), 2214 (2C≡N), 1722 (C=O), 1650 (3C=O), 1612 (C=N). ^{1}H-NMR (DMSO-d_6, δ): 1.24 (t, 3H, J = 6.0 Hz, CH_2CH_3), 3.80 (s, 3H, CH_3O), 4.34 (q, 2H, J = 7.4 Hz, CH_2CH_3), 5.59 (s, 1H, methine proton), 6.91-6.98 (m, 3H, Ar-H), 7.32-7.45 (m, 4H, Ar-H), 7.75-7.84 (m, 4H, Ar-H), 8.01 (d, 1H, J = 7.6 Hz, Ar-H), 8.37 (s, 1H, H-$2_{chromone}$), 13.46 (s, 1H, NH exchangeable with D_2O), 13.85 (s, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{38}H_{24}N_6O_7$ (676.65): C, 67.45; H, 3.58; N, 12.42%. Found C, 67.27; H, 3.68; N, 12.02%.

Ethyl 9-(4-chlorophenyl)-3-[(4-oxo-4H-chromen-3-yl)methylidene]-8-cyano-2-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-)-4,7-dioxo-4,5,6,7-tetrahydropyrido[1,2-b][1,2,4]triazepine-10-carboxylate (32)

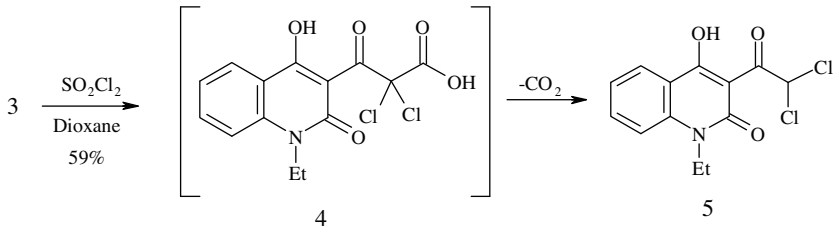
A mixture of compound **20** (0.41 g, 1 mmol) and ethyl 1,6-diamino-4-(4-chlorophenyl)-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate (**30**) (0.33 g, 1 mmol) in ethanol containing a few drops of triethylamine was heated under reflux for 4 h. The solid deposited during heating was filtered and crystallized from DMF to give compounds **32** as yellow crystals, yield (0.45 g, 62%), mp > 300 °C. IR (KBr, cm^{-1}): 3400 (OH), 3195 (NH), 3087 ($CH_{arom.}$), 2985, 2925 ($CH_{aliphatic}$), 2216 (C≡N), 1742 (C=O_{ester}), 1669 (4C=O), 1617 (C=N), 764 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ): 1.20 (t, 3H, J = 6.8 Hz, CH_2CH_3), 1.29 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.25 (q, 2H, J = 6.8 Hz, NCH_2CH_3), 4.38 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 5.62 (s, 1H, methine proton), 7.30 (t, 1H, J = 7.4 Hz, Ar-H), 7.49-7.54 (m, 4H, Ar-H), 7.75-7.91 (m, 5H, Ar-H), 8.06-8.12 (m, 2H, Ar-H), 8.84 (s, 1H, H-$2_{chromone}$), 13.47 (s, 2H, NH and OH exchangeable with D_2O). Anal. Calcd for $C_{39}H_{26}ClN_5O_8$ (728.10).C, 64.33; H, 3.60; N, 9.62; Cl, 4.87%. Found C, 64.15; H, 3.68; N, 9.52; Cl, 4.87%.

Results and discussion

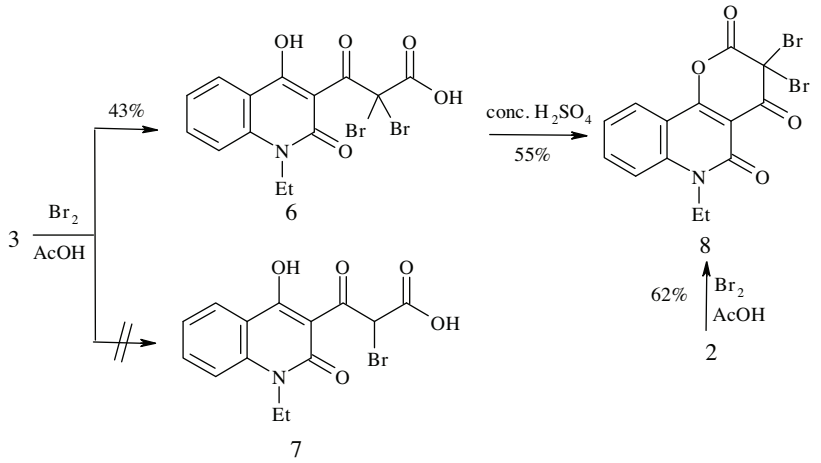
In continuation of our previous work on the chemical reactivity of 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid **(3)**,[14] chlorination of β-ketoacid **3** using sulfuryl chloride in dioxane afforded 3-(2,2-dichloroacetyl)-1-ethyl-4-hydroxyquinolin-2(1H)-one (**5**) via the nonisolable intermediate **4** (Scheme 2). Compound **5** was found to be identical to the authentic sample obtained from chlorination of 3-acetyl-4-hydroxyquinolin-2(1H)-one as previously published.[15,16] The ^{1}H-NMR spectrum of compound **5** showed a characteristic singlet at δ 7.87 ppm attributed to the $CHCl_2$ proton.

On the other hand, bromination of **3** using bromine in acetic acid under reflux afforded only the 2,2-dibromo-3-oxopropanoic acid derivative **6**.[17] Structure of the monobromo derivative **7** was ruled out on the basis of elemental analysis and spectral data (Scheme 3). The ^{1}H-NMR spectrum of compound **6** confirmed the absence of the 2 protons of the active methylene group, which appeared at δ 5.56 ppm in the β-ketoacid

3.[14] Moreover, the elemental analysis agrees well with the molecular formula $C_{14}H_{11}Br_2NO_5$, which proves the presence of 2 bromine atoms.



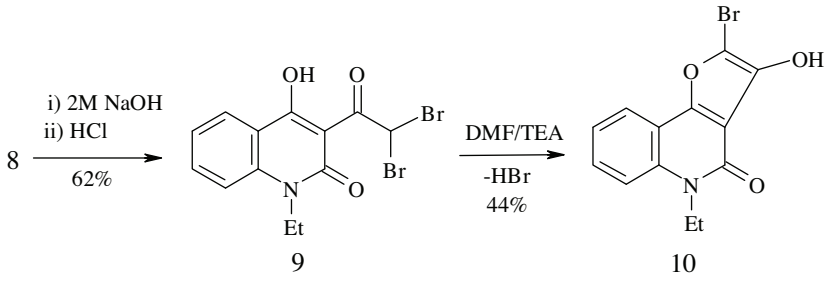
Scheme 2. Chlorination of β-ketoacid **3**.



Scheme 3. Bromination of compounds **2** and **3**.

Dehydration reaction of **6** by stirring in conc. H_2SO_4 at room temperature afforded 3,3-dibromo-6-ethylpyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**8**) (Scheme 3). The latter compound was obtained authentically in one pot from bromination of pyranoquinolinone **2** under the same reaction conditions [bromine in acetic acid] (Scheme 3). The broad signal due to the 2OH protons in compound **6** (which appeared at δ 14.42 ppm) did not appear in the ^{1}H-NMR spectrum of compound **8**. The mass spectrum of the dibromopyrano[3,2-*c*]quinoline derivative **8** did not show the molecular ion peak at m/z 415 but showed a peak at m/z 335 corresponding to the molecular ion after loss of one atom of bromine; this may be attributed to the steric effect between the 2 bromine atoms. The spectrum also revealed the base peak at m/z 172 assigned to the *N*-ethylquinolin-2(1*H*)-one moiety.

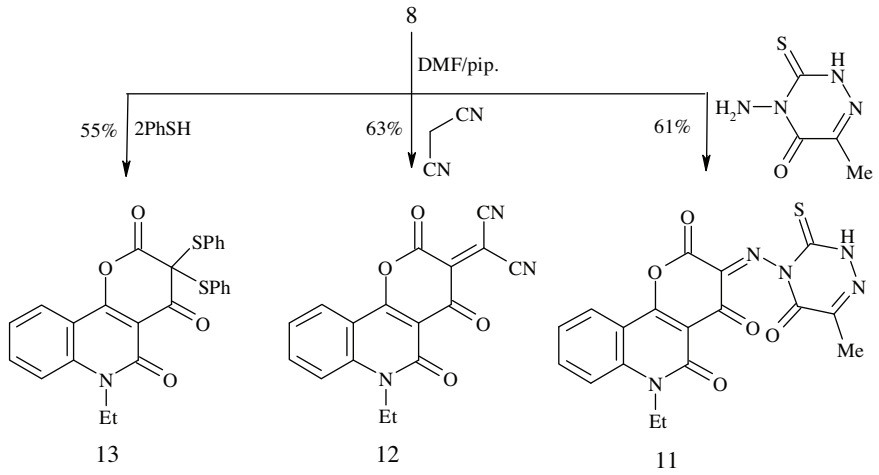
Basic hydrolysis of dibromopyrano[3,2-*c*]quinoline derivative **8** using 2 M aqueous NaOH solution yielded 3-(dibromoacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**9**) (Scheme 4). The IR spectrum of compound **9** did not reveal the α-lactone (OC=O) absorption band that appeared at 1730 cm^{-1} in the IR spectrum of compound **8**. The ^{1}H-NMR spectrum of the dibromoacetyl derivative **9** showed, in addition to the aromatic and ethyl protons, a characteristic singlet signal at δ 6.40 ppm due to the dibromoacetyl proton. Formation of compound **9** takes place via the hydrolytic ring opening of the dibromopyran ring system in compound **8** followed by decarboxylation.[16]



Scheme 4. Formation of dibromoacetylquinolinone **9** and furoquinolinone **10**.

Heterocyclization of dibromoacetylquinolinone **9** in boiling DMF containing a few drops of triethylamine (TEA) resulted in loss of one molecule of HBr to produce 2-bromo-5-ethyl-3-hydroxyfuro[3,2-*c*]quinolin-4(5*H*)-one (**10**) (Scheme 4). The ^{1}H-NMR spectrum of compound **10** showed the disappearance of the characteristic singlet signal attributable to the $CHBr_2$ proton, which appeared at δ 6.40 ppm in compound **9**.

Compound **8** was used as a good precursor to get some new pyrano[3,2-*c*]quinoline derivatives via reactions with a variety of nucleophilic reagents. Thus, condensation of **8** with 4-amino-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one[18] in boiling DMF containing a few drops of piperidine resulted in the loss of 2 molecules of HBr to produce 1,2,4-triazinyliminopyrano[3,2-*c*]quinoline derivative **11** (Scheme 5). The ^{1}H-NMR spectrum of compound **11** showed a characteristic singlet signal at δ 2.67 ppm assigned to the methyl protons, in addition to one exchangeable signal at δ 13.43 ppm due to $NH_{triazine}$ proton.

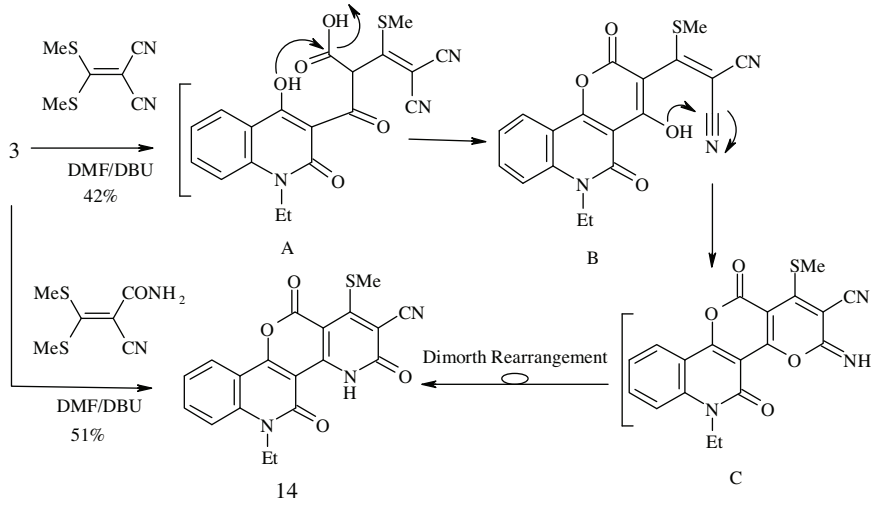


Scheme 5. Nucleophilic substitution reactions of dibromoquinolinone **8**.

Similarly, condensation of **8** with malononitrile under the same reaction conditions gave pyrano[3,2-*c*]quinolin-3-ylidenemalononitrile derivative **12**. The IR spectrum of compound **12** showed a characteristic absorption band due to the nitrile functions at 2207 cm^{-1}.

Furthermore, condensation of dibromo derivative **8** with 2 molecules of thiophenol in boiling DMF containing a few drops of piperidine gave *bis*-phenylsulfanyl-pyrano[3,2-*c*]quinoline derivative **13** (Scheme 5).[19] The mass spectrum of compound **13** showed the molecular ion peak at m/z 472 (M-1) and the base peak at m/z 239. The elemental analysis agrees well with the molecular formula $C_{26}H_{19}NO_4S_2$.

In the present investigation, we found that the reaction of β-ketoacid **3** with *bis*(methylthio)methylene-malononitrile and/or *bis*(methylthio)methylene-cyanoacetamide in boiling DMF containing a few drops of 1,8-diazabicycle[5.4.0]undec-7-ene (DBU) as a basic catalyst afforded one product, **14** (the same mp, mmp, and spectral data), and the reaction was expected to proceed as depicted in Scheme 6.[20] The reaction takes place initially via loss of one molecule of CH_3SH to give intermediate **A** with concomitant cyclization to afford intermediate **B**. The OH group of the pyrone ring, in intermediate **B**, undergoes nucleophilic addition to the nitrile function to yield iminopyran intermediate **C**, which undergoes Dimorth rearrangement [in the case of *bis*(methylthio)methylene-malononitrile] under the reaction conditions to give the final product identified as 6-ethyl-1-(methylsulfanyl)-3,5,12-trioxo-4,5,6,12-tetrahydro-3*H*-pyrido[2',3':4,5]pyrano[3,2-*c*]quinoline-2-carbonitrile (**14**). The IR spectrum of compound **14** showed characteristic absorption bands at 2196, 1743, 1673, and 1642 cm^{-1} attributed to C≡N, OC=O, C=$O_{quinolinone}$, and C=$O_{pyridone}$, respectively. Moreover, the mass spectrum of compound **14** showed the molecular ion peak at m/z 379, which is in good agreement with the formula weight (379.40) and supports the identity of the structure.

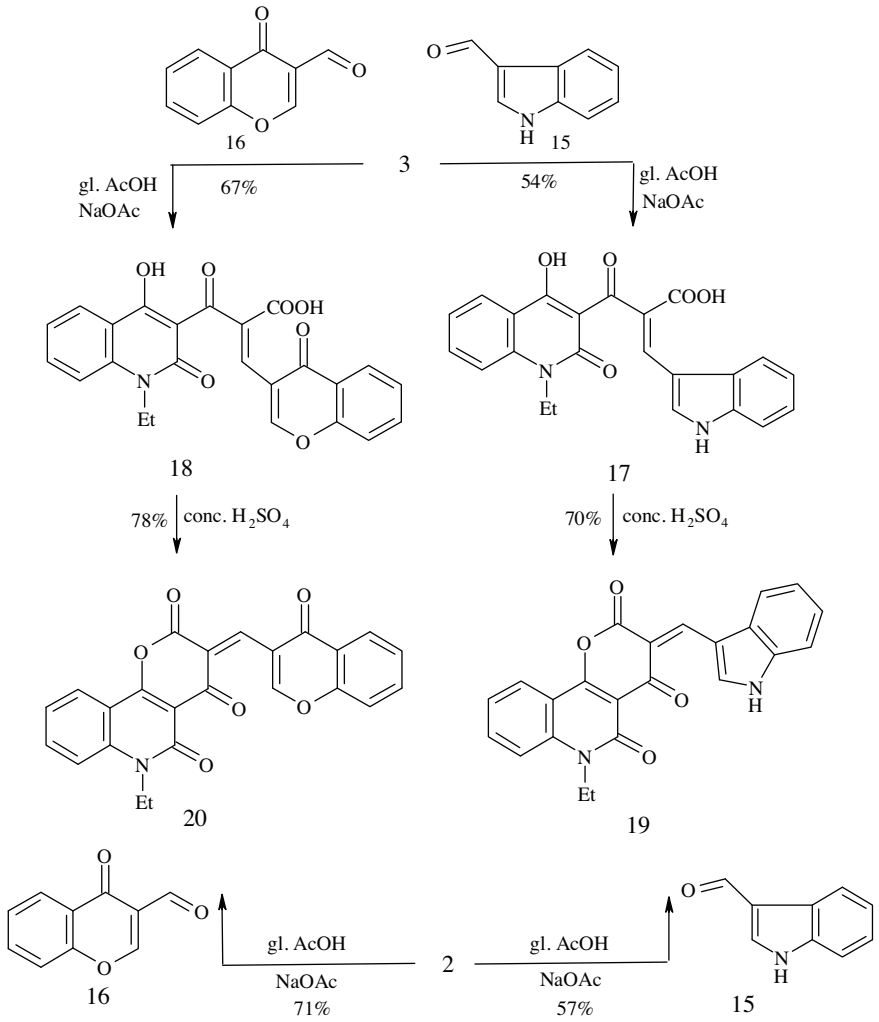


Scheme 6. Formation of pyrido[2',3':4,5]pyrano[3,2-*c*]quinoline **14**.

Knoevenagel condensation reactions characterized to the active methylene group in β-ketoacid **3** were studied towards some heterocyclic aldehydes. Therefore, condensation of compound **3** with 3-formylindole (**15**) and 3-formylchromone (**16**)[21] in glacial acetic acid containing freshly fused sodium acetate yielded the Knoevenagel condensation products **17** and **18**, respectively. The latter compounds gave positive acidity and $FeCl_3$ tests indicting the presence of free carboxylic and phenolic OH groups. The ^{1}H-NMR spectrum of compound **17** revealed the presence of 3 exchangeable signals at δ 9.93 (NH_{indole}), 12.14 (OH_{acid}), and 13.80 ppm ($OH_{quinolinone}$), while the ^{1}H-NMR spectrum of compound **18** revealed the presence of 1 exchangeable signal at δ 13.90 ppm assigned to $OH_{quinolinone}$ and OH_{acid}, in addition to a characteristic singlet signal at δ 8.93 ppm assigned to the H-2 of the chromone moiety.

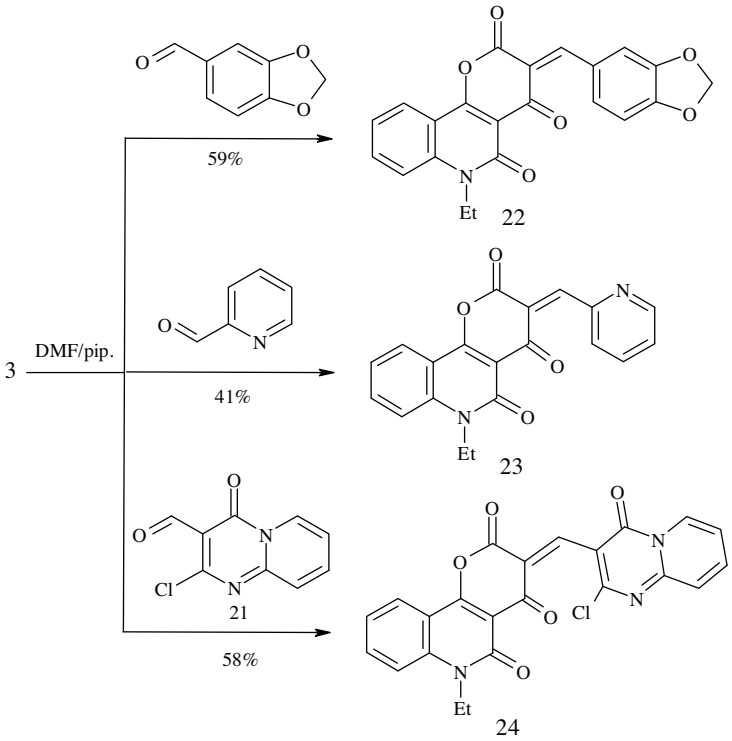
Heterocyclization of compounds **17** and **18** via dehydration reactions by stirring in concentrated H_2SO_4 at room temperature gave 3-substituted-pyrano[3,2-*c*]quinoline derivatives **19** and **20**, respectively (Scheme 7). Moreover, compounds **19** and **20** were obtained authentically from condensation reactions of pyrano[3,2-

c]quinoline **2** with 3-formylindole (**15**) and 3-formylchromone (**16**), respectively (Scheme 7). The ^{1}H-NMR spectrum of compound **20** showed 2 characteristic singlet signals at δ 8.35 and 8.81 ppm due to $CH_{methine}$ and H-$2_{chromone}$, respectively. Furthermore, the mass spectrum of compound **20** showed the molecular ion peak at m/z 413, which agrees well with the molecular mass and supports the identity of the structure.



Scheme 7. Condensation of compounds **2** and **3** with 3-formylindole (**15**) and 3-formylchromone (**16**).

Interestingly, condensation of β-ketoacid **3** with piperonal, 2-formylpyridine, and 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxaldehyde (**21**)[22] in boiling DMF containing a few drops of piperidine furnished directly the cyclized products, 3-(1,3-benzodioxol-5-ylmethylidene)-6-ethyl-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**22**), 6-ethyl-3-(pyridin-2-ylmethylidene)-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**23**), and 3-[(2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methylidene]-6-ethyl-2*H*-pyrano[3,2-*c*]quinoline-2,4,5 (3*H*,6*H*)-trione (**24**), 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 **22**-**24** (Scheme 8). The IR spectra of compounds **22**-**24** showed characteristic absorption bands attributed to O-C=O groups at 1737, 1739, and 1730 cm^{-1}, respectively.



Scheme 8. Condensation of **3** with some aldehyde derivatives.

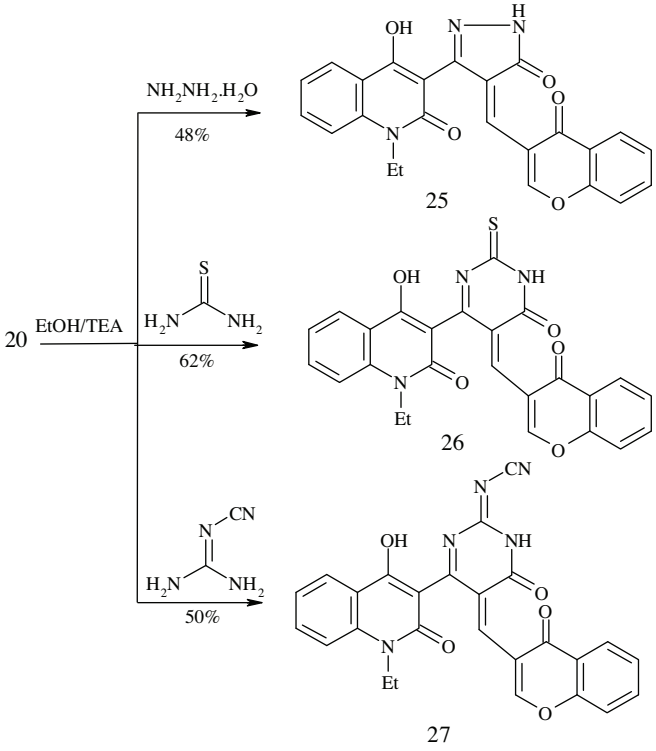
It is known that[23,24] α-pyrones are important synthons for the building of different classes of bioactive nitrogen heterocyclic compounds that are widely used in pharmaceutics. In the present study, we planned to prepare 4-hydroxyquinolinones bearing different nitrogen heterocycles linked chromone moiety in one molecular frame. Therefore, the chemical reactivity of chromenylmethylidene-pyrano[3,2-*c*]quinoline derivative **20** was studied towards some bifunctional nitrogen nucleophiles.

Treatment of **20** with hydrazine hydrate in ethanol containing a few drops of triethylamine resulted in α-pyrone ring opening followed by ring closure (RORC) with loss of one molecule of water leading to chromenylmethylidene-1*H*-pyrazolylquinolinone **25** (Scheme 9). The latter compound was found to be identical to the authentic sample previously prepared from the condensation of pyrazolylquinolinone with 3-formylchromone.[25] The ^{1}H-NMR spectrum of compound **25** showed exchangeable signal due to $NH_{pyrazole}$ and $OH_{quinolinone}$ at δ 13.78 ppm.

Reaction of **20** with thiourea and cyanoguanidine as 1,3-binucleophiles in ethanol containing a few drops of triethylamine afforded the pyrimidine derivatives **26** and **27**, respectively (Scheme 9). Herein again, the ^{1}H-NMR spectra of compounds **26** and **27** showed characteristic singlet signals assigned to the methine protons and H-2 of chromone moiety, in addition to the $NH_{pyrimidine}$ and $OH_{quinolinone}$ protons as exchangeable signals. Moreover, the IR spectrum of compound **26** showed a characteristic absorption band due to the thioxo group at 1219 cm^{-1}, while that of compound **27** showed a characteristic absorption band due to the nitrile function at 2176 cm^{-1}.

Reaction of **20** with *o*-phenylenediamine gave a benzodiazepine derivative identified as 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-[(4-oxo-4*H*-chromen-3-yl)methylidene])-1,3-dihydro-2*H*-1,5-benzo-

diazepin-2-one (**28**) (Scheme 10). The ^{1}H-NMR spectrum of compound **28** showed characteristic singlet signals assigned to the methine proton and H-2$_{chromone}$ at δ 5.83 and 8.80 ppm, respectively, in addition to the NH$_{diazepine}$ and OH$_{quinolinone}$ protons at δ 12.54 and 13.60 ppm, respectively. The mass spectrum of **28** did not show the molecular ion peak at m/z 503 but showed a peak at m/z 419 corresponding to the molecular ion after the loss of 3 carbonyl groups.



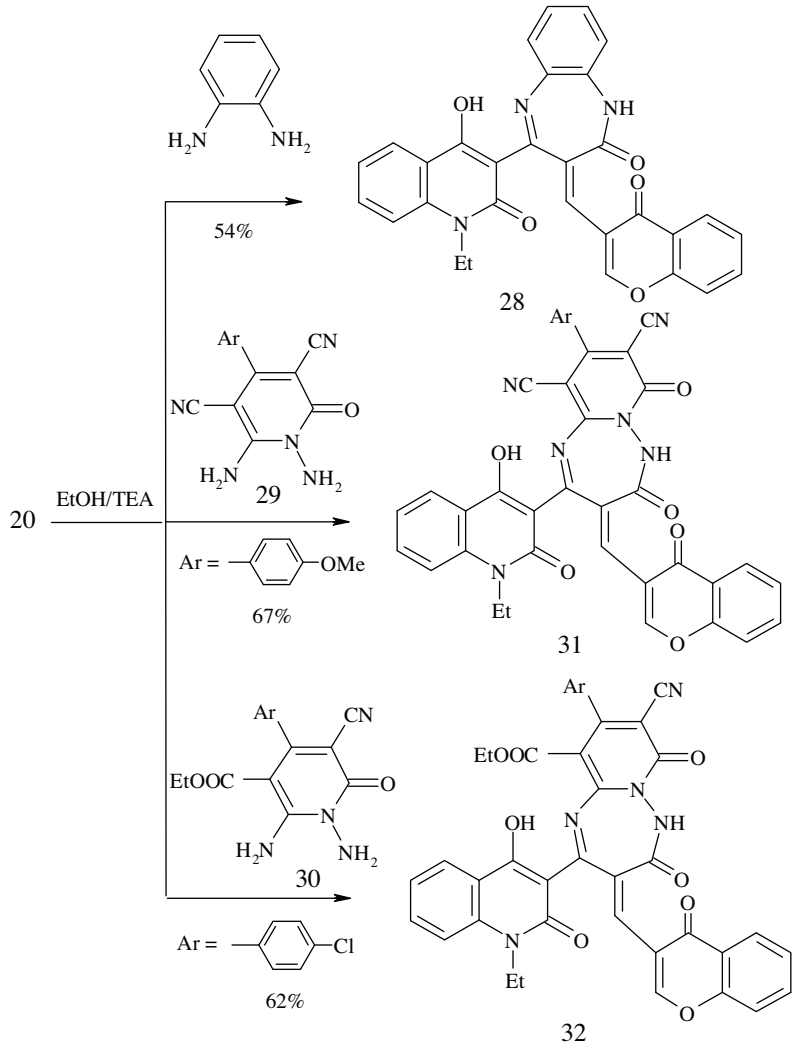
Scheme 9. RORC reactions of compound **20**; formation of **25-27**.

Herein again, reaction of **20** with 1,6-diaminopyridine derivatives **29** and **30**[26] as 1,4-bifunctional nucleophiles afforded the pyrido[1,2-*b*][1,2,4]triazepine derivatives **31** and **32**, respectively (Scheme 10). The reactions proceeds initially via α-pyrone ring opening by the more nucleophilic amino group (N-NH$_2$) followed by ring closure to produce the desired products **31** and **32**.[27]

Antimicrobial activity

The standardized disk agar diffusion method[28] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* as gram-positive bacteria, *Proteus vulgaris* as gram-negative bacteria, and *Candida albicans* as fungal strain. The antibiotics Doxymycin and Fluconazole were purchased from Egyptian markets and used in concentrations of 100 μg mL^{-1} as references for antibacterial and antifungal activities.

The compounds were dissolved in DMSO, which has no inhibition activity, to obtain a concentration of 100 μg mL^{-1}. The test was performed on medium potato dextrose agars (PDAs) containing an infusion of 200



Scheme 10. RORC reactions of compound **20**; formation of **28**, **31**, and **32**.

g of potatoes, 6 g of dextrose, and 15 g of agar.[29] The results depicted in the Table showed various activities against all species of microorganisms, which suggests that the variations in the structures affect the growth of the microorganisms. Thus, we can conclude from these results:

1. Most of the prepared compounds showed a low to high antimicrobial activity towards gram-positive bacteria, gram-negative bacteria and the fungal strain (Table).

2. Compounds **3**, **11**, **18**, and **22** showed higher activity than the standard antibiotic Doxymycin against *Staphylococcus aureus* as gram-positive bacteria.

3. Compound **17** showed equal activity to the standard antibiotic Doxymycin against *Proteus vulgaris* as gram-negative bacteria, while compounds **3**, **6**, **11**, **12**, and **22** showed higher activity.

4. Compound **12** showed higher activity than the standard Fluconazole as fungal strain.

As a result, compounds **3**, **6**, **11**, **12**, **17**, **18**, and **22** may be considered promising for the development of new antimicrobial agents.

Table. The antimicrobial activity of the newly synthesized compounds.

Compound No.	Diameter of inhibition zone (mm) conc. (100 μg mL^{-1})		
	S. aureus (gram +ve)	*P. vulgaris* (gram -ve)	*C. albicans* (Fungal strain)
3	20	15	8
6	7	12	11
8	6	8	-
9	-	-	-
10	-	-	-
11	35	20	6
12	-	15	17
13	-	-	-
14	-	-	13
17	10	10	13
18	18	7	9
19	-	8	-
20	-	8	-
22	18	28	9
23	11	-	-
24	-	-	10
25	-	-	-
26	-	-	12
27	-	-	-
28	-	-	-
31	7	-	-
32	-	-	-
Doxymycin	15	10	-
Fluconazole	-	-	16

"-" means no activity

Conclusion

In the present work, some novel 4-hydroxyquinolin-2(1*H*)-ones and pyrano[3,2-*c*]quinolin-2(1*H*)-ones were successfully synthesized starting from 3-(1-ethy1-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**3**). The antimicrobial activities of the prepared compounds showed that quinolinone derivatives **3**, **6**, **11**, **12**, **17**, **18**, and **22** have good inhibitory effects towards bacterial and fungal strains.

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