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SYNTHESIS OF SUBSTITUTED QUINOLINONE KETONES DERIVED WITH SOME FIVE, SIX, AND SEVEN-MEMBERED HETEROCYCLES

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Abstract: The synthesis of a series of new quinolinyl ketones substituted with some five-, six-, and seven-membered diaza-heterocycles is described. Efficient base- or acid-catalyzed nucleophilic heterocyclization of 6-ethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxaldehyde with a variety of nitrogen and/or carbon 1,2-, 1,3-, and 1,4-binucleophiles afforded the target ketones in good yields. The structure of all new products was established on basis of their spectral and analytical data.

Keywords: Pyrano[3,2-c]quinolines, quinolinyl ketones, nucleophilic reactions, heterocyclization.

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Introduction

Pyrano[3,2-c]quinolines are known as good precursors of many biologically important substituted quinolinones. Pyranoquinoline derivatives possess a variety of biological activities such as psychotropic, antiallergenic, anti-inflammatory, and estrogenic activity [1]. Quinolinone derivatives are of increasing interest due to their useful biological properties such as antiparasitic [2-5], antimicrobial [6], enzymatic enhancement [7,8], antibacterial, antifungal [9-11], antiproliferative, antitubulin [12], anti-hepatitis B-virus (HBV) [13,14], and anti-HIV-1 activities [15]. Furthermore, 3-formyl-γ-pyrones, such as 3-formylchromones, show interesting synthetic properties as starting material for various heterocyclic systems. This is due to their availability for nucleophilic reactions in which these compounds possess three electron-deficient sites, *viz.*; α-position of pyrone, γ-position of pyrone, and aldehydic C=O [16-21]. The center C-2 is very reactive towards Michael addition of nucleophiles which, in proper cases, is accompanied by γ-pyrone ring-opening and ring closure (RORC) to give a new heterocyclic system [22-26].

Herein we aimed to synthesize and use 6-ethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxaldehyde **(1)**, in which the molecular-frame contains the quinolinone nucleus derived with the reactive 3-formyl-γ-pyrone moiety, as a starting material. We report the study of its chemical reactivity towards a variety of nucleophilic reagents, hoping to get a series of 4-hydroxyquinolin-2(1H)-ones bearing miscellaneous heterocyclic systems of expected biological activity.

Experimental

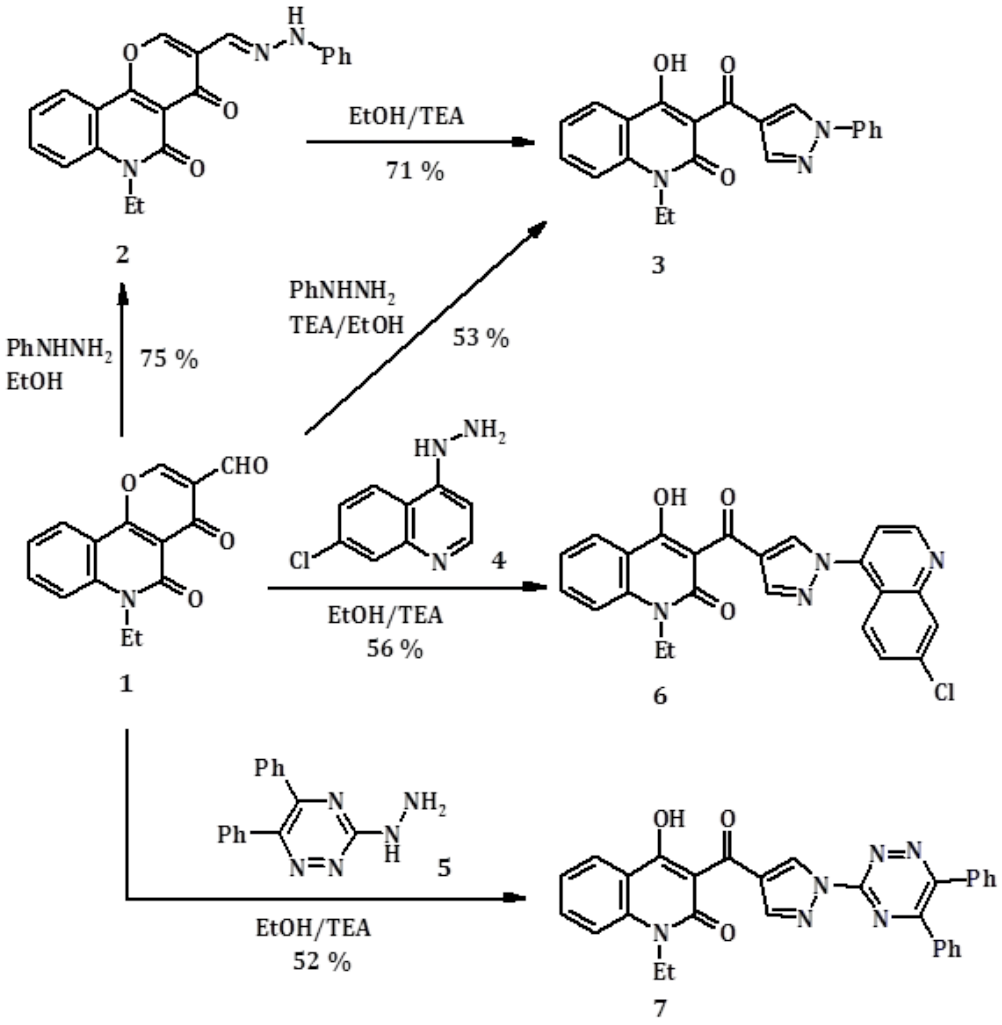
General

Melting points were determined on a digital Stuart SMP3 apparatus. Fourier transform infrared spectra were taken on FT-IR Nicolet IS10 spectrophotometer (ν cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Mass spectrometry was measured using GC-2010 Shimadzu Gas chromatograph (70 eV) GC-MS QP-1000 EX Shimadzu mass spectrometer. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

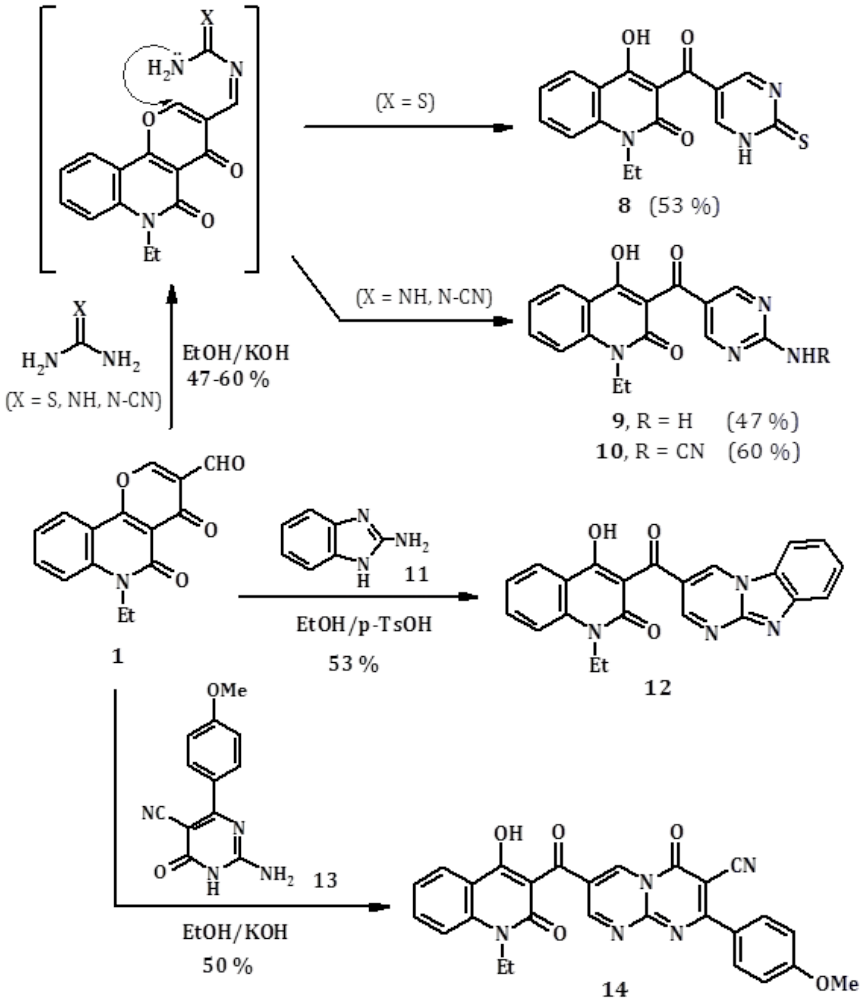
6-Ethyl-3-[(2-phenylhydrazinylidene)methyl]-4H-pyrano[3,2-c] quinoline-4,5(6H)-dione (2)

A mixture of aldehyde **(1)** (0.54 g, 2 mmol) and phenylhydrazine (0.22 mL, 2 mmol) was refluxed for 2 h. The solid obtained after cooling was filtered and crystallized from ethanol to give compound 2 as brown crystals, yield (0.54 g, 75%), mp 243–244 °C.

FT-IR (KBr, cm^{-1}): 3336 (NH), 3035 (CH_{arom}), 2972, 2930 (CH_{aliph}), 1646 ($C=O_{\gamma\text{-pyrone}}$), 1636 ($C=O_{quinolone}$), 1600 (C=N) and 1580 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.09 (t, 3H, J = 6.6 Hz, CH_2CH_3), 4.19 (q, 2H, J=6.6 Hz, CH_2CH_3), 6.62 (t, 1H, J=7.2 Hz, H_{arom}), 6.79 (d, 1H, J=7.2 Hz, H_{arom}), 7.03 (t, 1H, J=7.2 Hz, H_{arom}), 7.17 (d, 1H, J=6.2 Hz, H_{arom}), 7.35 (t, 1H, J=7.2 Hz, H_{arom}), 7.44 (d, 1H, J=7.8 Hz, H_{arom}), 7.56 (t, 1H, J=6.2 Hz, H_{arom}), 7.84 (t, 1H, J=7.2 Hz, H_{arom}), 8.03 (d, 1H, J=6.9 Hz, H_{arom}), 8.08 (s, 1H, CH=N), 8.35 (s, 1H, H-2) and 9.91 (s, 1H, NH exchangeable with D_2O). MS, m/z(%): 359 $[M]^{\cdot+}$(not detected), 357 $[M - H_2]^{\cdot+}$(14), 238 (4), 144 (2), 119 (5), 116 (7), 103 (2), 60 (100) and 52 (2). Anal. Calcd. for $C_{21}H_{17}N_3O_3$ (359.38); C, 70.18; H, 4.77; N, 11.69%. Found: 70.02; H, 4.58; N, 11.62%.



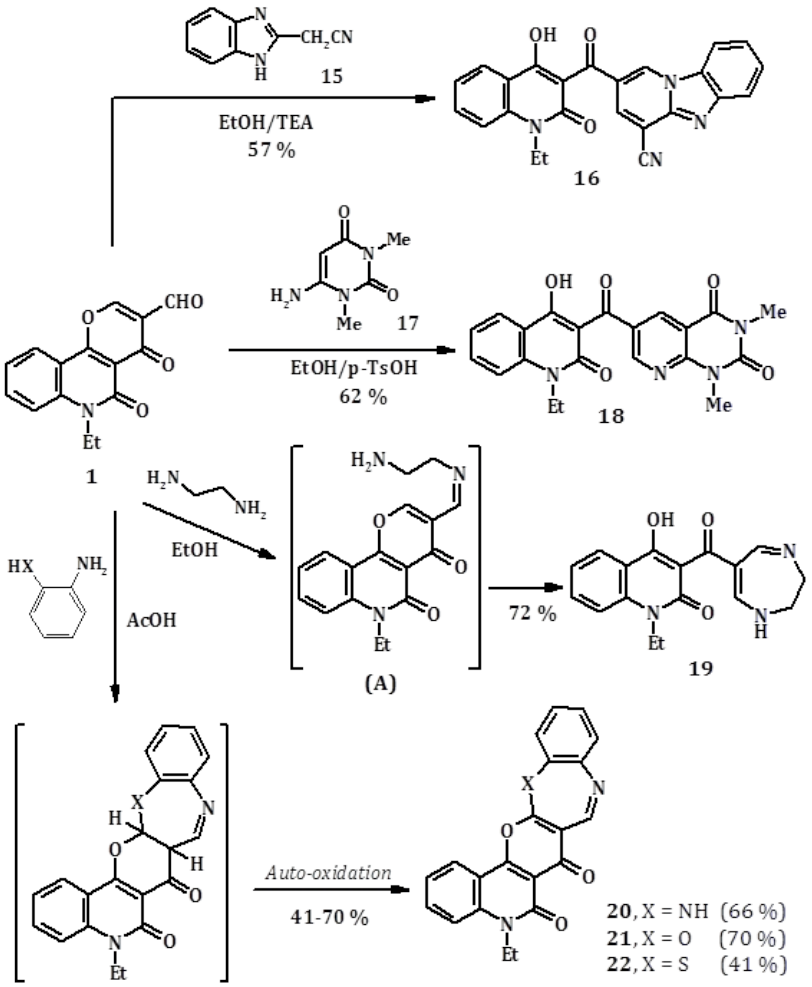
Scheme 1. Reaction of aldehyde 1 with some hydrazine derivatives.



Scheme 2. Formation of some pyrimidylquinolinone derivatives.

1-Ethyl-4-hydroxy-3-[(1-phenyl-1H-pyrazol-4-yl)carbonyl] quinolin-2(1H)-one (3)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and phenylhydrazine (0.22 mL, 2 mmol) in absolute ethanol (20 mL) containing few drops of triethylamine was refluxed for 2 h. The solid obtained after cooling was filtered and crystallized from ethanol to give compound **3** as orange crystals, yield (0.38 g, 53%), mp 189–190 °C. FT-IR (KBr, cm^{-1}): 3280 (OH), 3025 ($CH_{arom.}$), 2978, 2940 ($CH_{aliph.}$), 1625 ($C=O_{quinolone}$ and C=O), 1599 (C=N) and 1585 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.23 (t, 3H, CH_2CH_3), 4.35 (q, 2H, CH_2CH_3), 6.55 (d, 1H, H_{arom}), 6.74 (d, 1H, H_{arom}), 6.93-7.63 (m, 6H, H_{arom}), 7.72 (s, 1H, H-$5_{pyrazole}$), 7.91 (d, 1H, H_{arom}) and 8.12 (s, 1H, H-$3_{pyrazole}$).MS, m/z(%): 359 $[M]^{\cdot+}$ (67), 188 (100). Anal. Calcd. for $C_{21}H_{17}N_3O_3$ (359.38); C, 70.18; H, 4.77; N, 11.69%. Found: C, 70.11; H, 4.71; N, 11.58%.



Scheme 3. Heterocyclization of compound 1 with some 1,3-and 1,4-binucleophiles.

The same product **3** (mp, mixed mp, and spectra) was also obtained (yield 0.14 g, 71%) when phenylhydrazone **2** (0.2 g, 0.6 mmol) was refluxed for 2 h, in absolute ethanol (10 mL), containing few drops of triethylamine.

1-Ethyl-4-hydroxy-3-[(1-(7-chloroquinolin-4-yl)-1H-pyrazol-4-yl) carbonyl]-quinolin-2(1H)-one (6)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 7-chloro-4-hydrazinoquinoline (**4**) (0.36 g, 2 mmol) in absolute ethanol (20 mL) containing few drops of triethylamine was heated under reflux for 2h. The solid obtained during heating was filtered and crystallized from DMF/H_2O to give compound **6** as orange-red crystals, yield (0.50 g, 56%), mp 203–204°C. FT-IR (KBr, cm^{-1}): 3447 (OH), 3065 ($CH_{arom.}$), 2978–2945 ($CH_{aliph.}$), 1636 ($C=O_{quinolone}$), 1628 ($C=O_{hydrogen\ bonded}$), 1612 (C=N) and 1593 (C=C).

^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.23 (t, 3H, J=7.5 Hz, CH_2CH_3), 4.27 (q, 2H, J=6.9 Hz, CH_2CH_3), 7.33 (t, 1H, J=7.2 Hz, H_{arom}), 7.63 (d, 1H, J= 8.7 Hz, H_{arom}), 7.75-7.82 (m, 3H, H_{arom}), 8.14 (d, 1H, J=7.8 Hz, H_{arom}), 8.24 (s, 1H, $H_{8quinoline}$), 8.34 (d, 1H, J=8.7 Hz, $H_{3quinoline}$), 8.45 (s, 1H, $H_{5pyrazole}$), 9.08 (d, 1H, J=8.1 Hz, $H_{2quinoline}$), 9.13 (s, 1H, $H_{3pyrazole}$) and 13.87 (bs, 1H, OH exchangeable with D_2O). MS, m/z(%):446 $[M]^{\cdot+}$ (27),444 (56), 415 (13), 256 (44), 229 (25), 228 (29), 216 (14), 189 (32), 178 (100), 172 (21), 166 (14), 165 (19), 151 (25), 142 (21), 130 (30), 104 (25), 80 (13), 78 (19) and 54 (16). Anal. Calcd. for $C_{24}H_{17}ClN_4O_3$ (444.87); C, 64.80; H, 3.85; N, 12.59%. Found: C, 64.66; H, 3.74; N, 12.38%.

1-Ethyl-4-hydroxy-3-[(1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1H-pyrazol-4-yl)-carbonyl]quinolin-2(1H)-one (7)

A mixture of aldehyde 1 (0.54 g, 2 mmol) and 3-hydrazino-5,6-diphenyl-1,2,4-triazine **(5)** (0.49 g, 2 mmol) in absolute ethanol (20 mL) containing few drops of triethylamine was heated under reflux for 2 h. The solid obtained after cooling was filtered and crystallized from methanol to give compound 7 as yellow crystals, yield (0.54 g, 52%), mp 226–227°C. FT-IR (KBr, cm^{-1}): 3191 (OH), 2976, 2945 ($CH_{aliph.}$), 1653 ($C=O_{quinolone}$ and $C=O_{hydrogen\ bond}$), 1618 (C=N) and 1591 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.23 (t, 3H, J=7.0 Hz, CH_2CH_3), 4.29 (q, 2H, J=7.5 Hz, CH_2CH_3), 7.33 (t, 1H, J= 7.8 Hz, H_{arom}), 7.39-7.55 (m, 10H, H_{arom}), 7.61 (d, 1H, H_{arom}), 7.78 (t, 1H, J=8.7 Hz, H_{arom}), 8.15 (d, 1H, J=7.8 Hz, H_{arom}), 8.45 (s, 1H, $H_{5pyrazole}$) and 9.47 (s, 1H, $H_{3pyrazole}$). MS, m/z(%): 514$[M]^{\cdot+}$ (13),299 (3), 283 (3), 254 (4), 238 (7), 227 (1), 215 (3), 187 (4), 178 (100), 172 (4), 165 (4), 151 (5), 145 (2), 142 (1), 132 (10), 119 (4), 104 (7), 91 (4), 77 (14) and 64 (4). Anal. Calcd. for $C_{30}H_{22}N_6O_3$ (514.53); C, 70.03; H, 4.31; N, 16.33%. Found: C, 69.85; H, 4.15; N, 16.08%.

1-Ethyl-4-hydroxy-3-[(2-thioxo-1,2-dihydropyrimidin-5-yl)carbonyl] quinolin-2(1H)-one (8)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and thiourea (0.15 g, 2 mmol) in ethanolic potassium hydroxide solution (20 mL, 1%) was refluxed for 4h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with dilute HCl. The precipitate so formed was filtered and crystallized from ethanol to give compound **8** as orange crystals, yield (0.35 g, 53%), mp 246–247°C. FT-IR (KBr, cm^{-1}): 3308 (O–H), 3165 (N–H), 2977, 2960 ($C–H_{aliph.}$), 1676 ($C=O_{quinolone}$), 1644 (C=O), 1616 (C=N), 1560 (C=C) and 1264 (C=S). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.23 (t, 3H, J=7.2 Hz, CH_2CH_3), 4.39 (q, 2H, J=7.2 Hz, CH_2CH_3), 6.84 (s, 1H, $H_{6pyrimidine}$), 7.49 (t, 1H, J=7.8 Hz, H_{6arom}), 7.82 (d, 1H, J=9.0 Hz, H_{8arom}), 7.91 (t, 1H, J=6.9 Hz, H_{7arom}), 8.21 (d, 1H, J=8.4 Hz, H_{5arom}), 8.60 (s, 1H, $H_{4pyrimidine}$) and 13.74 (b, 2H, NH and OH exchangeable with D_2O).

MS, m/z(%): 327[M]$^{\cdot+}$(3),310 (19), 282 (4), 254 (2), 215 (2), 187 (3), 144 (2), 139 (2), 132 (4), 116 (1), 111 (3), 104 (2), 103 (2), 91 (3), 77 (8), 59 (100), and 52 (3). Anal. Calcd. for $C_{16}H_{13}N_3O_3S$ (327.36); C, 58.70; H, 4.00; N, 12.84; S, 9.80%. Found: C, 58.61; H, 4.02; N, 12.79; S, 9.72%.

3-[(2-Aminopyrimidin-5-yl)carbonyl]-1-ethyl-4-hydroxyquinolin-2(1H)-one (9)

A mixture of aldehyde 1 (0.54 g, 2 mmol) and guanidine hydrochloride (0.19 g, 2 mmol) in ethanolic potassium hydroxide solution (20 mL, 1%) was refluxed for 4 h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with concentrated HCl. The precipitate so formed was filtered and crystallized from DMF to give compound **9** as pale brown crystals, yield (0.29 g, 47%), mp 249–250°C. FT-IR (KBr, cm^{-1}): 3420 (OH, NH_2), 2977, 2930 (CH_{aliph}), 1652 ($C=O_{quinolone}$ and $C=O_{ketone}$), 1610 (C=N) and 1563 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.25 (t, 3H, J=6.9 Hz, CH_2CH_3), 4.26 (q, 2H, J =6.9 Hz, CH_2CH_3), 7.39 (t, 1H, J=7.5 Hz, H_{6arom}), 7.56 (d, 1H, J=8.4 Hz, H_{8arom}), 7.70-7.79 (m, 1H, H_{7arom}), 7.86 (s, 1H, $H_{6pyrimidine}$), 7.98 (s, 1H, $H_{4pyrimidine}$), 8.05 (d, 1H, J=6.9 Hz, H_{5arom}) and 8.36 (bs, 2H, NH_2 exchangeable with D_2O). MS, m/z(%): 310[M]$^{\cdot+}$(not detected), 308 [M–H_2]·+(5), 265 (20), 237 (14), 189 (20), 178 (100), 161 (11), 132 (31), 122 (12), 119 (15), 95 (12), 77 (33), 67 (18), 65 (8) and 51 (41). Anal. Calcd. for $C_{16}H_{14}N_4O_3$ (310.31); C, 61.93; H, 4.55; N, 18.06%. Found: C, 61.85; H, 4.34; N, 18.01%.

3-[(2-Cyanoaminopyrimidin-5-yl)carbonyl]-1-ethyl-4-hydroxy quinolin-2(1H)-one (10)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and cyanoguanidine (0.17 g, 2 mmol) in ethanolic potassium hydroxide solution (20 mL, 1%) was heated under reflux for 4h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with concentrated HCl. The precipitate so formed was filtered and crystallized from ethanol to give compound **10** as pale brown crystals, yield (0.40 g, 60%), m.p 235–236 °C. FT-IR (KBr, cm^{-1}): 3428 (OH, NH), 3030 ($CH_{arom.}$), 2973, 2955 ($CH_{aliph.}$), 2161 (C≡N), 1671 ($C=O_{quinolone}$), 1636 ($C=O_{hydrogen\text{-}bonded}$), 1613 (C=N) and 1558 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.22 (t, 3H, J=6.9 Hz, CH_2CH_3), 4.34 (q, 2H, J = 6.9 Hz, CH_2CH_3), 7.31 (t, 1H, J=6.9 Hz, H_6), 7.59 (d, 1H, J=8.8 Hz, H_8), 7.76 (t, 1H, J=6.9 Hz, H_7), 8.09 (d, 1H, J=7.6 Hz, H_5), 8.80 (s, 1H, $H_{6pyrimidine}$), 8.82 (s, 1H, $H_{4pyrimidine}$), 10.11 (bs, 1H, NH exchangeable with D_2O) and 13.31 (bs, 1H, OH exchangeable with D_2O). MS, m/z(%): 335 [M]$^{\cdot+}$ (12), 307 [M– CO]$^{\cdot+}$ (100),Anal. Calcd. for $C_{17}H_{13}N_5O_3$ (335.32); C, 60.89; H, 3.91; N, 20.89%. Found: C, 60.82; H, 3.84; N, 20.75%.

1-Ethyl-4-hydroxy-3-(pyrimido[1,2-a]benzimidazol-3-ylcarbonyl) quinolin-2(1H)-one (12)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 2-aminobenzimidazole **(11)** (0.27 g, 2 mmol) in absolute ethanol (20 mL) containing one crystal of p-toluenesulfonic acid was heated under reflux for 4h. The solid obtained during heating was filtered and crystallized from DMF to give compound **12** as pale yellow crystals, yield (0.41 g, 53%), mp 276–277 °C. FT-IR (KBr, cm^{-1}): 3420 (O–H), 3073 ($CH_{arom.}$), 2980, 2940 ($CH_{aliph.}$), 1633 ($C=O_{quinolone}$), 1629 ($C=O_{hydrogen\ bond}$), 1605 (C=N) and 1585 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.22 (t, 3H, J=6.6 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.2 Hz, CH_2CH_3), 7.32 (t, 1H, J=6.8 Hz, H_{arom}), 7.43-7.86 (m, 5H, H_{arom}), 8.12 (d, 1H, H_{arom}), 8.45 (d, 1H, H_{arom}), 9.04 (s, 1H, $H_{4\text{-pyrimidine}}$) and 9.96 (s, 1H, $H_{2\text{-pyrimidine}}$). MS, m/z(%): 384 $[M]^{\cdot+}$(33),216 (1), 215 (2), 200 (100), 196 (7), 189 (12), 169(21), 168 (13), 160 (6), 145 (13), 142 (6), 132 (40), 119 (7), 118 (10), 116 (7), 104 (25), 91 (10) and 77 (38). Anal. Calcd. for $C_{22}H_{16}N_4O_3$ (384.39); C, 68.74; H, 4.20; N, 14.58%. Found: C, 68.65; H, 4.13; N, 14.46%.

7-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)carbonyl]-2-(4-methoxyphenyl)-4-oxo-4H-pyrimido[1,2-a]pyrimidine-3-carbonitrile (14)

A mixture of aldehyde 1 (0.54 g, 2 mmol) and 2-amino-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **(13)** (0.49 g, 2 mmol) in ethanolic po-tassium hydroxide solution (20 mL, 1%) was refluxed for 4h. After cooling at room temperature, the reaction mixture was poured onto crushed ice and neutralized with dilute HCl. The precipitate so formed was filtered and crystallized from DMF to give compound **14** as yellow crystals, yield (0.49 g, 50%), mp 204–205 °C. FT-IR (KBr, cm^{-1}): 3341 (OH), 3080 ($CH_{arom.}$), 2934, 2860 ($CH_{aliph.}$), 2167 (C≡N), 1677 ($C=O_{pyrimidone}$), 1643 ($C=O_{quinolone}$), 1636 ($C=O_{hydrogen\ bond}$), 1613 (C=N) and 1586 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.09 (t, 3H, J=6.9 Hz, CH_2CH_3), 3.78 (s, 3H, OCH_3), 4.11 (q, 2H, CH_2CH_3), 6.98-7.11 (m, 5H, H_{arom} & $H_{pyrimidine}$), 7.24 (d, 1H, J=6.9 Hz, H_{arom}), 7.41 (d, 1H, J=8.7 Hz, H_{arom}), 7.84 (d, 1H, J=8.7 Hz, H_{arom}), 7.95 (d, 1H, J=7.8 Hz, H_{arom}) and 8.16 (s, 1H, $H_{pyrimidine}$). MS, m/z(%): 493 $[M]^{\cdot+}$ (2), 188 (100). Anal. Calcd. for $C_{27}H_{19}N_5O_5$ (493.47); C, 65.72; H, 3.88; N, 14.19%. Found: C, 65.58; H, 3.57; N, 14.03%.

2-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)carbonyl] pyrido[1,2-a]benzimidazole-4-carbonitrile (16)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 2-(1H-benzimidazol-2-yl)acetonitrile **(15)** (0.32 g, 2 mmol) in absolute ethanol containing few drops of TEA was heated under reflux for 4h. The solid obtained after cooling was filtered and crystallized from DMF/EtOH to give compound **16** as pale brown crystals, yield (0.47 g, 57%), mp 275–276°C.

FT-IR (KBr, cm^{-1}): 3055 (CH_{arom}), 2984, 2881 (CH_{aliph}), 2231 (C≡N), 1647 ($C=O_{quinolone}$), 1640 (C=O), 1588 (C=N), and 1558 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.22 (t, 3H, J=6.9 Hz, CH_2CH_3), 4.24 (q, 2H, J=6.9 Hz, CH_2CH_3), 7.35 (t, 1H, J=7.2 Hz, H_{arom}), 7.50 (t, 1H, J=7.2 Hz, H_{arom}), 7.62-7.67 (m, 2H, H_{arom}), 7.78 (t, 1H, J=7.2 Hz, H_{arom}), 7.96 (d, 1H, J=8.1 Hz, H_{arom}), 8.15 (d, 1H, J=7.8 Hz, H_{arom}), 8.57 (s, 1H, $H_{2pyridine}$), 8.60 (d, 1H, H_{arom}), 9.89 (s, 1H, $H_{4pyridine}$). MS, m/z(%):408 $[M]^{\cdot+}$ (100), 380 (15), 364 (6), 352 (11), 220 (15), 193 (65), 192 (29), 189 (8), 187 (11), 172 (11), 160 (13), 144 (7), 132 (19), 119 (9), 118 (15), 117 (6), 104 (10), 91 (8), 90 (22), 77 (37) and 63 (25).Anal. Calcd. for $C_{24}H_{16}N_4O_3$ (408.41); C, 70.58; H, 3.95; N, 13.72%. Found: C, 70.33; H, 3.73; N, 13.65%.

6-[(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)carbonyl]-1,3-dimethylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (18)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 6-amino-1,3-dimethyluracil **(17)** (0.31 g, 2 mmol) in absolute ethanol (20 mL) containing one crystal of p-toluenesulfonic acid was heated under reflux for 30 min. The solid obtained during heating was filtered and crystallized from DMF/EtOH to give compound **18** as yellow crystals, yield (0.51 g, 62%), mp > 300 °C. FT-IR (KBr, cm^{-1}): 3446 (OH), 2976, 2870 ($CH_{aliph.}$), 1714 ($C=O_{pyrimidone}$), 1665 ($C=O_{pyrimidone}$), 1647 ($C=O_{quinolone}$), 1625 (C=O), 1606 (C=N), 1580 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.17 (t, 3H, J=6.9 Hz, CH_2CH_3), 3.62 (s, 3H, N-CH_3), 3.72 (s, 3H, N-CH3), 4.22 (q, 2H, J=6.9 Hz, CH_2CH_3), 7.34 (t, 1H, J=7.8 Hz, H-6_{arom}), 7.73 (d, 1H, J=9 Hz, H-8_{arom}), 7.77 (t, 1H, J=7.2 Hz, H-7_{arom}), 8.11 (d, 1H, J=7.8 Hz, H-5_{arom}), 8.55 (s, 1H, H-$4_{pyridine}$) and 9.02 (s, 1H, H-$2_{pyridine}$). ^{13}C NMR (75 MHz, DMSO) δ (ppm):12.6, 28.1, 29.3, 36.6, 109.5, 114.8, 121.7, 123.7, 123.9, 124.9, 129.1, 133.3, 136.9, 139.3, 139.9, 150.8, 152.4, 154.2, 158.4, 160.5, 193.3. MS, m/z(%):406 $[M]^{\cdot+}$ (33), 405 (100), 389 (20), 378 (13), 377 (43), 218 (13), 161 (17), 133 (17), 132 (37), 119 (17), 104 (17), 77 (40) and 76 (27). Anal. Calcd. for $C_{21}H_{18}N_4O_5$ (406.39); C, 62.06; H, 4.46; N, 13.79%. Found: C, 61.84; H, 4.22; N, 13.67%.

3-[(2,3-Dihydro-1H-1,4-diazepin-6-yl)carbonyl]-1-ethyl-4-hydroxyquinolin-2(1H)-one (19)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and ethylenediamine (0.12 mL, 2 mmol) in absolute ethanol (20 mL) was heated under reflux for 15 min. The solid obtained during heating was filtered and crystallized from DMF to give compound **19** as yellow crystals, yield (0.45 g, 72%), mp 284–285 °C. FT-IR (KBr, cm^{-1}): 3420 (OH, NH), 2973, 2927, 2870 ($CH_{aliph.}$), 1663 ($C=O_{quinolone}$), 1645 ($C=O_{hydrogen\ bonded}$), 1617 (C=N), and 1587 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.12 (t, 3H, J=6.9 Hz, CH_2CH_3), 3.69 (m, 4H, NCH_2-CH_2N), 4.11 (q, 2H, J=6.9 Hz, CH_2CH_3), 6.95 (t, 1H, J=6.9 Hz, H-6_{arom}), 7.23 (d, 1H, J=8.4, H-8_{arom}), 7.41 (t, 1H, J=7.2 Hz, H-7_{arom}), 7.97 (d, 1H, J=7.8 Hz, H-5_{arom}) and 8.17 (s, 2H, H-$5_{diazepine}$& H-$7_{diazepine}$).

MS, m/z(%): 311 $[M]^{\cdot+}$ (21),294 $[M- OH]^+$ (100), 279 (2), 216 (33), 200 (10), 188 (19), 172 (11), 160 (4), 144 (6), 132 (45), 123 (12), 116 (9), 104 (22), 96 (48), 95 (19), 77 (51) and 65 (18). Anal. Calcd. for $C_{17}H_{17}N_3O_3$ (311.34); C, 65.58; H, 5.50; N, 13.50%. Found: C, 65.36; H, 5.39; N, 13.28%.

5-Ethyl-14H-quinolino[3',4':5,6]pyrano[2,3-b][1,5]benzo diazepine-6,7(5H)-dione (20)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 1,2-phenylenediamine (0.22 g, 2 mmol) in glacial acetic acid was refluxed for 30 min. The solid obtained during heating was filtered and crystallized from DMF to give compound **20** as orange crystals, yield (0.48 g, 66%), mp 292–293 °C. FT-IR (KBr, cm^{-1}): 3246 (NH), 2979, 2965 ($CH_{aliph.}$), 1651 ($C=O_{\gamma\text{-pyrone}}$ and $C=O_{quinolone}$), 1618 (C=N) and 1558 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.23 (t, 3H, CH_2CH_3), 4.26 (q, 2H, CH_2CH_3), 7.17 (t, 1H, H_{arom}), 7.38 (d, 1H, H_{arom}), 7.49-7.78 (m, 4H, H_{arom}), 8.08 (d, 1H, H_{arom}), 8.36 (s, 1H, CH=N) and 8.69 (d, 1H, H_{arom}). MS, m/z(%): 357 $[M]^{\cdot+}$ (not detected), 356 $[M - H]^+$(19), 341 (17), 330 (14), 279 (20), 261 (15), 235 (16), 174 (16), 166 (24), 140 (23), 125 (31), 105 (31), 91 (24), 77 (12), 64 (41) and 55 (100). Anal. Calcd. for $C_{21}H_{15}N_3O_3$ (357.36); C, 70.58; H, 4.23; N, 11.76%. Found: C, 70.42; H, 4.21; N, 11.48%.

5-Ethylquinolino[3',4':5,6]pyrano[2,3-b][1,5]benzoxazepine-6,7(5H) -dione (21)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 2-aminophenol (0.22 g, 2 mmol) in glacial acetic acid (15 mL) was refluxed for 2h. The solid so formed after cooling was filtered and crystallized from DMF to give compound **21** as orange-red crystals, yield (0.5 g, 70%), mp 284–285 °C. FT-IR (KBr, cm^{-1}): 2950, 2915 (CH_{aliph}), 1648 ($C=O_{\gamma\text{-pyrone}}$), 1633 ($C=O_{quinolone}$), 1617 (C=N) and 1570 (C=C). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.19 (t, 3H, CH_2CH_3), 4.26 (q, 2H, CH_2CH_3), 6.95-7.92 (m, 8H, H_{arom}), 8.11 (s, 1H, CH=N). MS, m/z(%): 358 $[M]^{\cdot+}$ (16), 241 (7), 216 (11), 189 (84), 172 (13), 161 (71), 145 (32), 132 (100), 119 (88), 116 (18), 104 (70), 94 (18), 91 (54), 77 (91) and 64 (62). Anal. Calcd. for $C_{21}H_{14}N_2O_4$ (358.35); C, 70.39; H, 3.94; N, 7.82%. Found: C, 70.17; H, 3.78; N, 7.65%.

5-Ethylquinolino[3',4':5,6]pyrano[2,3-b][1,5]benzothiazepine-6,7(5H)-dione (22)

A mixture of aldehyde **1** (0.54 g, 2 mmol) and 2-aminothiophenol (0.25 mL, 2 mmol) in glacial acetic acid was heated under reflux for 2 h. The solid obtained after cooling was filtered and crystallized from DMF to give compound **22** as pale brown crystals, yield (0.31 g, 41%), mp 280–281 °C. FT-IR (KBr, cm^{-1}): 3070 (CH_{arom}), 2973, 2931 ($CH_{aliph.}$), 1682 ($C=O_{\gamma\text{-pyrone}}$), 1645 ($C=O_{quinolone}$), 1610 (C=N) and 1584 (C=C).

^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.22 (t, 3H, J=6.6 Hz, CH_2CH_3), 4.27 (q, 2H, J=6.6 Hz, CH_2CH_3), 7.28-7.51 (m, 5H, H_{arom}), 7.64 (d, 1H, J=8.7 Hz, H_{arom}), 7.83 (t, 1H, J=7.5 Hz, H_{arom}), 8.09 (d, 1H, J=8.1 Hz, H_{arom}), 8.61 (s, 1H, CH=N). MS, m/z(%): 374 $[M]^{\cdot+}$ (not detected), 373 $[M–H]^+$ (4), 271 (4), 241 (6), 216 (10), 213 (5), 200 (4), 189 (9), 161 (9), 145 (6), 135 (4), 132 (17), 119 (8), 116 (6), 110 (100), 104 (6), 91 (13), 77 (50), 64 (23). Anal. Calcd. for $C_{21}H_{14}N_2O_3S$ (374.41); C, 67.37; H, 3.77; N, 7.48; S, 8.56%. Found: C, 67.24; H, 3.56; N, 7.32; S, 8.41%.

Results and Discussion

Recently, we have described a convenient synthesis of 6-ethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxaldehyde **(1)** [27]. The structure of aldehyde **1** comprises variable electron-deficient centers and expected to be quite reactive towards nucleophilic reagents [28]. The chemical reactivity of aldehyde **1**, towards a variety of nitrogen and carbon nucleophiles, was disclosed, in order to obtain some novel 4-hydroxyquinolinones bearing a diverse heterocyclic system of expected biological activity. Therefore, treatment of aldehyde **1** with phenylhydrazine, in absolute ethanol, gave the corresponding phenylhydrazone **2**, in 75% yield, while when this reaction was carried out, in boiling ethanol containing triethylamine (TEA), phenylpyrazole derivative **3** was obtained, in 53% yield. This reaction may take place via first formation of phenylhydrazone **2**, followed by intramolecular γ-pyrone RORC to give pyrazole **3** [29]. However, this hypothesis was supported via transformation of phenylhydrazone **2** into pyrazole **3** by action of TEA, in boiling ethanol, in 71% yield (Scheme 1). Structures of phenylhydrazone **2** and phenylpyrazole **3** were confirmed on the basis of their spectral data. FT-IR spectrum of phenylhydrazone **2** displayed characteristic absorption bands at 1646, 1636 cm^{-1} attributed to ($C=O_{\gamma\text{-pyrone}}$) and ($C=O_{quinolone}$). These two carbonyl absorption vibrations lie in a lower frequency region due to delocalization of lone pair of electrons. These observations are in good agreement with the literature values [30, 31]. ^{1}H NMR spectrum of phenylhydrazone **2** showed two singlet signals at δ 8.08 and 8.35, attributed to $H_{azomethine}$ and H-2, respectively. In addition, a deuterium exchangeable proton appeared at δ 9.91, as singlet signal due to chemical shift of N–H proton [32]. ^{1}H NMR spectrum of phenylpyrazole **3** revealed two singlet signals at δ 7.72 and 8.12 characteristic for the pyrazole protons [33].

Similarly, when aldehyde **1** was reacted with the commercially available 7-chloro-4-hydrazinoquinoline **(4)** and/or 3-hydrazino-5,6-diphenyl-1,2,4-triazine **(5)** [34] in boiling ethanol containing TEA, the respective pyrazoles **6** and **7**, were afforded in more than 50% yields (Scheme 1). ^{1}H NMR spectra of both pyrazoles **6** and **7** showed two singlet signals distinguishable for 1,4-disubstituted pyrazole aromatic protons at δ 8.45 and 9.13, in compound 6 and 8.45 and 9.47, in compound **7**.

These signals appeared at higher downfield than known 1H-pyrazole, a phenomenon which may be attributed to deshielding effects of both substations at positions 1 and 4 [35]. The mass spectra of compounds **6** and **7** showed their molecular ion peaks at m/z 444 and 514, respectively.

Interestingly, reaction of aldehyde **1** with a variety of 1,3-N,N-binucleophilic reagents; such as thiourea, guanidine and cyanoguanidine, may lead to formation of pyrimidine derivatives [36]. Thus, treatment of aldehyde **1** with thiourea, guanidine hydrochloride and cyanoguanidine, in ethanolic potassium hydroxide solution, gave the corresponding pyrimidine derivatives **8-10**, in 47-60% yields (Scheme 2). The formation of pyrimidine derivatives **8-10** may take place initially *via* nucleophilic addition of the NH_2 group of 1,3-diaza-nucleophile to the aldehydic group followed by elimination of water molecule to give azomethine intermediate which in turn may undergo intramolecular nucleophilic attack, by the second NH_2, at position 2 of the γ-pyrone moiety. At this step, the pyrone nucleus undergoes RORC, leading to pyrimidine ring system [37]. The FT-IR spectrum of compound **10** showed characteristic absorption band at 2161 cm^{-1}, which can be attributed to the nitrile function [38]. ^{1}H NMR spectra of compounds **8-10** showed characteristic singlet signals attributed to H-$4_{pyrimidine}$ and H-$6_{pyrimidine}$. In addition, ^{1}H NMR spectrum of compound **9** showed an exchangeable signal at δ 8.36, which is attributed to chemical shift of NH_2 protons [38].

Also, the condensation of aldehyde 1 with 2-aminobenzimidazole **(11)**, using a catalytic amount of p-toluenesulfonic acid, furnished 1-ethyl-4-hydroxy-3-(pyrimido[1,2-a]benzimidazol-3-yl-carbonyl)quinolin-2(1H)-one **(12)**, in 53% yield (Scheme 2). Carrying out the same reaction under base catalysis conditions as described before led to lower yields (~ 10–12%). This may be explained by weakness of nucleophilicity of 2-aminoimidazole in which the reaction can be catalyzed with an acid to facilitate removal of water. This case is similar to Friedländer reaction which can be either acid or base catalyzed [39]. The reaction takes place *via* the non-isolable Schiff's base intermediate which undergoes RORC leading to ketone **12**. The FT-IR spectrum indicated absorption vibrations at 1633 (C=$O_{quinolone}$), 1629 (C=O) and 1605 cm^{-1} (C=N). ^{1}H NMR spectrum of compound **12** showed characteristic chemical shifts of pyrimidine protons, at positions 4 and 6, appeared as two singlets at δ 9.04 and 9.96. Further, the mass spectrum showed a molecular ion peak at m/z 384, which is coincident with the calculated most abundant isotope of $M^{+\cdot}$, supporting the suggested formula.

Similarly, condensation of aldehyde 1 with 2-amino-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**13**) [23], in ethanolic potassium hydroxide solution, afforded pyrimido[1,2-a]pyrimidine-3-carbonitrile **14**, in 50% yield (Scheme 2). The FT-IR spectrum of compound **14** showed absorption bands at 2167 (C≡N), 1677 (C=$O_{pyrimidone}$), 1643 (C=$O_{quinolone}$), 1636 (C=O) and 1613 cm^{-1} (C=N).

To obtain new quinolinone derivatives bearing functionalized pyridinyl substituents, aldehyde **1** was subjected to react with a variety of 1,3-binucleophilic reagents. Treatment of aldehyde **1** with 2-(1H-benzimidazol-2-yl)acetonitrile **(15)**, in presence of TEA as a basic catalyst, provided pyrido[1,2-a]benzimidazole-4-carbonitrile **16**, in 57% yield (Scheme 3). The reaction proceeds via nucleophilic addition-elimination (condensation) of the active methylene group with the aldehyde function leading to alkene intermediate which undergoes, *in situ*, intramolecular nucleophilic attack at position 2 of γ-pyrone ring with concomitant ring opening [37]. Structural evidence for compound **16** was achieved from the FT-IR spectrum which showed characteristic absorption band at 2231 cm^{-1} assigned to (C≡N) function. ^{1}H NMR spectrum presented two singlet sets δ 8.57 and 9.89 specific to pyridine protons. Mass spectrum revealed the molecular ion peak, as the base peak, at m/z 408 which agreed well with its suggested molecular formula.

Treatment of aldehyde 1 with 6-amino-1,3-dimethyluracil **(17)**, in absolute ethanol containing catalytic amount of p-toluenesulfonic acid, furnished pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione **(18)**, in 62% yield (Scheme 3). The FT-IR spectrum presented absorption bands at 1714 ($C=O_{pyrimidone}$), 1665 ($C=O_{pyrimidone}$), 1647 ($C=O_{quinolone}$), and 1625 cm^{-1} (C=O). ^{1}H NMR spectrum showed chemical shifts for different N-alkyl protons; N-ethyl set of protons appeared at δ 1.17 (t, NCH_2CH_3) and 4.22 (q, NCH_2CH_3), in addition to two N-methyl protons ($N\text{-}CH_3$) appeared as two singlets at δ 3.62 and 3.72 [38]. Also, the spectrum indicated the presence of four aromatic protons in the range δ 7.34–8.11 characteristic for benzo protons of quinoline, in addition to pyridine protons which appeared as singlet peaks at higher downfield chemical shifts δ 8.55 and 9.02 [37]. Mass spectrum revealed the molecular ion peak at m/z 406 along with $[M-H]^+$ cation appeared as base peak at m/z 405. ^{13}C NMR spectrum revealed the aliphatic methyl and ethyl carbons at δ 12.6, 28.1, 29.3 and 36.6, besides other skeletal carbons.

The chemical reactivity of aldehyde **1** was studied towards different 1,4-binucleophiles. Thus, the condensation of carboxaldehyde **1** with ethylenediamine in absolute ethanol produced 1,4-diazepinylcarbonylquinolin-2(1H)-one 19, in 72% yield. The reaction proceeds via the formation of the corresponding Schiff's base intermediate A followed by an intramolecular nucleophilic addition at C-2 position with concomitant γ-pyrone ring opening to produce the final product **19** (Scheme 3). The FT-IR spectrum of compound **19** showed characteristic absorption bands at 3200 (N–H), 1663 ($C=O_{quinolone}$), 1645 (C=O) and 1617 cm^{-1} (C=N) [37]. The mass spectrum showed the molecular ion peak at m/z 311 corresponding to the formula weight (311.34) and the base peak at m/z 294, due to $[M-OH]^+$ ion.

Surprisingly, aromatic 1,4-biheteroatom nucleophiles gave stable pentacyclic heteroannulated compounds. Condensation of aldehyde 1 with 1,2-phenylenediamine, 2-aminophenol and 2-aminothiophenol, in glacial acetic acid, gave quinolino[3',4':5,6]pyrano[2,3-b][1,5]benzodiazepine **20**, quinolino[3',4':5,6] pyrano[2,3-b][1,5]benzoxazepine **21**, and quinolino[3',4':5,6]pyrano [2,3-b][1,5]benzothiazepine **22**, in 41-70% yields (Scheme 3). It is thought that obtaining aromatized pentacyclic compounds **20–22** was accomplished via condensation of the amino group with the aldehyde group, producing the non-isolable Schiff's base intermediate, followed by intramolecular addition of the rest neighboring heteroatom to position 2 of γ-pyrone ring. The products revealed that autoxidation took place during the course of reaction leading to aromatization of the pentacyclic fused systems.

Conclusions

The results show that many quinolinyl ketones attached to five, six, and seven-membered diaza-heterocycles are conveniently obtained starting from 6-ethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxaldehyde. This key compound pyrano[3,2-c]quinoline was found objectively reactive enough against 1,2-, 1,3-, and 1,4-binucleophiles, to undergo RORC, leading to the anticipated heterocyclic products, in moderate to good yields (41-72%). The reaction of pyrano[3,2-c]quinoline with binucleophiles was found, in most cases, to be base-catalyzed while in certain lesser reactive binucleophiles acid catalyst, such as p-toluenesulfonic acid, can lead to satisfactory yields.

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Türkçe öz ve anahtar kelimeler

BAZI BEŞ, ALTI VE YEDİ ÜYELİ HETEROHALKALARDAN TÜRETİLEN SÜBSTİTÜE KİNOLİNON KETONLARIN SENTEZİ

Öz: Bazı beş, altı ve yedi üyeli diaza-heterohalkalarla sübstitüe edilmiş bir seri yeni kinolinil ketonların sentezi bildirilmiştir. 6-etil-4,5-diokso-5,6-dihidro-4H-pirano[3,2-c]kinolin-3-karboksaldehidin bir seri azot ve/veya karbonlu 1,2-, 1,3- ve 1,4-binükleofillerle etkili baz veya asit katalizli nükleofilik heterohalkalaşması, hedeflenen ketonları iyi verimlerle oluşturmuştur. Bütün yeni ürünlerin yapıları spektral ve analitik verilere dayanarak ortaya konmuştur.

Anahtar kelimeler: Pirano[3,2-c]kinolinler, kinolinil ketonlar, nükleofilik tepkimeler, heterohalkalaşma.