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CHEMICAL REACTIVITY OF ETHYL 4-(1-ETHYL-1,2-DIHYDRO-4-HYDROXY-2-OXOQUINOLIN-3-YL)-2,4-DIOXOBUTANOATE TOWARDS SOME NUCLEOPHILIC REAGENTS

Magdy A. Ibrahim[1], Hany M. Hassanin[1]*, and Shimaa Badran[1]

[1]*Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Heliopolis 11757, Cairo, Egypt.*

Abstract: A novel series of heterocyclic systems linked with quinolin-2-one was efficiently synthesized from reaction of ethyl 4-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-2,4-dioxobutanoate (**1**) with a variety of nitrogen and/or carbon nucleophiles. A variety of heterocyclic systems such as pyrazoles, pyrimidines, pyrazines, oxazines and triazines containing quinoline moiety were synthesized. Structures of the new synthesized products were deduced on basis of their analytical and spectral data.

Keywords: Quinolin-2-one, diketoester, active methylene, nucleophilic reaction, heterocyclization.
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Correspondence to: Hany M. Hassanin. E-mail: hanyhassnin@yahoo.com.

INTRODUCTION

4-Hydroxyquinolin-2(1H)-ones represent one of the most important classes of heterocycles possessing a wide spectrum of biological activities [1-4]. Quinoline derivatives have been used as bactericidal [5], anti-inflammatory [6], antimalarial [7], antitumor [8], antioxidant [9], antileishmanial [10] and antiplatelet activities [11] such as DNA binding capabilities and DNA-intercalating carrier [12]. Also, a broad number of important pharmacological activities have been associated with 3-substituted 4-hydroxyquinolin-2(1H)-ones [13, 14]. The present work aimed to synthesize ethyl 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate (**1**) [15] as a starting material and study its chemical reactivity towards a variety of nucleophilic reagents, in a hope to obtain a novel series 4-hydroxyquinolin-2(1H)-ones bearing variable heterocyclic systems of expected biological activity.

EXPERIMENTAL SECTION

General. Melting points were determined on a digital Stuart SMP3 apparatus. Fourier-transform infrared spectra were taken on FT-IR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR (300 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Mass spectra were measured using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV) GC-MS qp 1000 ex Shimadzu instrument (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer at the Chemical War Department, Ministry of Defense, Egypt. Ethyl 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate (**3**) [15] was prepared according to the literature method.

Ethyl 1-(2-cyanoacetyl)-5-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-1H-pyrazole-3-carboxylate (3).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and cyanoacetohydrazide (0.15 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was stirred at room temperature for 2 h. The beige precipitate so formed was filtered and crystallized from EtOH to give compound **3** as beige crystals, yield (0.30 g, 54%), m.p. > 300 ^oC. FT-IR (KBr, cm^{-1}): 3446 (OH), 2987, 2934 ($CH_{aliph.}$), 2263 (C≡N), 1756 ($C=O_{ester}$), 1695 ($C=O_{ketone}$), 1638 ($C=O_{quinolone}$), 1572 (C=N) and 1504 (C=C). ^1H NMR (δ, 300 MHz, DMSO-d_6): 1.16-1.32 (m, 6H, $2CH_2CH_3$), 3.90 (s, 2H, CH_2), 4.19 (q, 2H, NCH_2CH_3), 4.48 (q, 2H, OCH_2CH_3), 7.20 (s, 1H, H-$4_{pyrazole}$), 7.32 (t, 1H, H-$6_{quinolone}$), 7.59 (d, 1H, H-$8_{quinolone}$), 7.72 (t, 1H, H-$7_{quinolone}$), 8.06 (d, 1H, H-$5_{quinolone}$), 11.90 (bs, 1H, OH exchangeable with D_2O). Mass spectrum, m/z (I_r %): 394 ($M^{+\cdot}$, 14), 393 (60), 363 (24), 368 (11), 327 (17), 268 (47), 230 (10), 212 (18), 197 (16), 188 (8), 172 (8), 161 (8), 146 (19), 132 (29), 119 (21), 102 (66), 91 (25), 77 (79), 64 (96) and 55 (100). Anal. Calcd. for $C_{19}H_{19}N_3O_5$ (394.38); C, 60.91; H, 4.60; N, 14.21%. Found: C, 60.80; H, 4.55; N, 14.08%.

Ethyl 5-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-1-[(pyridine-3-yl) carbonyl]-1H-pyrazole-3-carboxylate (4).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and nicotinic acid hydrazide (0.21 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 2 h. The brown crystals deposited after cooling were filtered and recrystallized from ethanol to give compound **4** as pale brown crystals, yield (0.24 g, 37%), m.p. > 300 ^{o}C; FT-IR (KBr) ν_{max} 3446 (OH), 2981, 2931 ($CH_{aliph.}$), 1706 ($C=O_{ester}$), 1683 ($C=O_{ketone}$), 1632 ($C=O_{quinolone}$), 1617 (C=N) and 1550 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18-1.30 (m, 6H, 2CH2C*H*$_3$), 4.10-4.25 (m, 4H, 2C*H*$_2$CH$_3$), 7.10 (s, 1H, H-4$_{pyrazole}$), 7.40-7.60 (m, 3H, H-6$_{quinolone}$, H-8$_{quinolone}$ and H-7$_{quinolone}$), 8.10 (d, 1H, H-5$_{quinolone}$), 8.30 (t, 1H, H-5$_{pyridine}$), 8.60-8.80 (m, 2H, H-4$_{pyridine}$ and H-6$_{pyridine}$), 8.90 (s, 1H, H-2$_{pyridine}$), 10.00 (bs, 1H, OH exchangeable with D_2O); Mass spectrum, m/z (rel. int. %): 432 [M$^{+\cdot}$] (6), 347 (3), 327 (6), 281 (5), 269 (4), 224 (4), 182 (9), 132 (6), 120 (5), 106 (37) and 64 (100). Anal. Calcd for $C_{23}H_{20}N_4O_5$ (432.44), C, 63.90%; H, 4.50%; N, 12.88%; Found, C, 63.88%, H, 4.66%, N, 12.96%.

Ethyl 1-(7-chloroquinolin-4-yl)-5-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-1H-pyrazole-3-carboxylate (5).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and 7-chloro-4-hydrazinoquinoline (**2**) (0.29 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 4 h. The reaction mixture was left to cool at room temperature. The solid so formed was filtered and crystallized from DMF to give compound **5** as red-brown crystals, yield (0.35 g, 47%), m.p. > 300 ^{o}C; FT-IR (KBr) ν_{max} 3406 (OH), 3076 ($CH_{arom.}$), 2931 ($CH_{aliph.}$), 1707 ($C=O_{ester}$), 1628 ($C=O_{quinolone}$), 1608 (C=N) and 1586 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300MHz) δ 1.19-1.22 (m, 6H, 2CH$_2$C*H*$_3$), 4.10-4.30 (m, 4H, 2C*H*$_2$CH$_3$), 6.40 (s, 1H, H-4$_{pyrazole}$), 7.12 (t, 1H, H-6$_{quinolone}$), 7.32-7.46 (m, 2H, H-8$_{quinolone}$ and H-6$_{quinoline}$), 7.46 (s, 1H, H-8$_{quinoline}$), 7.6 (t, 1H, H-7$_{quinolone}$), 7.60-8.00 (m, 2H, H-5$_{quinolone}$ and H-5$_{quinoline}$), 8.15 (d, 1H, H-2$_{quinoline}$), 8.32 (d, 1H, H-3$_{quinoline}$); Mass spectrum, m/z (rel. int. %): 489 [M$^{+\cdot}$] (67), 464 (91), 432 (77), 417 (97), 352 (80), 319 (83), 272 (65), 229 (95), 206 (97), 178 (100) and 77 (76). Anal. Calcd for $C_{26}H_{21}ClN_4O_4$ (488.93), C 63.70%; H 4.40%; N 11.36%; found, C 63.87%; H 4.33%; N 11.46%.

Ethyl 5-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)[1,2,4]triazolo[4,3-*a*] pyrimidine-7-carboxylate (7).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and 3-amino[1,2,4]triazole (**6**) (0.13 g, 1.51 mmol), in absolute ethanol (20 mL) containing few drops of acetic acid, was heated under reflux for 4 h. The yellow crystals deposited after cooling were filtered and crystallized from EtOH to give compound **7** as golden yellow crystals, yield (0.38 g, 67%), m.p. 200-201 ^{o}C; FT-IR (KBr) ν_{max} 3447 (OH), 3103 ($CH_{arom.}$), 2970, 2925, 2854 ($CH_{aliph.}$), 1751 ($C=O_{ester}$), 1635 ($C=O_{quinolone}$), 1609 (C=N) and 1570 cm^{-1} (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.21 (t, 3H, *J*=6.9 Hz, N-CH$_2$C*H*$_3$), 1.38 (t, 3H, *J*=6.7 Hz, O-CH$_2$C*H*$_3$), 4.24 (q, 2H, *J*=6.9 Hz, N-C*H*$_2$CH$_3$), 4.50 (q, 2H, *J*=6.7 Hz, O-C*H*$_2$CH$_3$), 7.20 (t, 1H, H-6$_{quinolone}$), 7.51 (d, 1H, H-8$_{quinolone}$), 7.60 (t, 1H, H-7$_{quinolone}$), 8.03 (d, 1H, J=6.7 Hz, H-5$_{quinolone}$), 8.73 (s, 1H, H-5$_{pyrimidine}$), 9.40 (s, 1H, H-3$_{triazole}$), 17 (bs, 1H, OH exchangeable with D_2O). Mass spectrum, m/z (rel. int. %): 379 [M$^{+\cdot}$] (95), 360 (61), 331 (71), 279 (67), 267 (67), 223 (84), 203 (61), 162 (69), 132 (100), 89 (47) and 77 (84). Anal. Calcd for $C_{19}H_{17}N_5O_4$ (379.38), C, 60.20%; H, 4.65%; N, 18.52%; found, C 60.15%; H 4.52%; N 18.46%.

Ethyl 4-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)pyrimido[1,2-*a*] benzimidazole-2-carboxylate (9).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and 2-aminobenzimidazole (**8**) (0.20 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 2 h. The orange-red crystals obtained during heating was filtered and crystallized from DMF to give compound **9** as orange-red, yield (0.50 g, 77%), m.p. > 300 °C; FT-IR (KBr) ν_{max} 3359 (OH), 3093 ($CH_{arom.}$), 2970, 2925 ($CH_{aliph.}$), 1707 ($C=O_{ester}$), 1645 ($C=O_{quinolone}$), 1612 (C=N) and 1588 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.19-1.24 (m, 6H, $2CH_2CH_3$), 4.20-4.30 (m, 4H, $2CH_2CH_3$), 6.90 (s, 1H, H-$3_{pyrimidine}$), 7.02-7.04 (m, 2H, Ar-H), 7.22-7.24 (m, 2H, Ar-H), 7.41 (t, 1H, *J*=7.5 Hz, H-$6_{quinolone}$), 7.64 (d, 1H, *J*=8.7 Hz, H-$8_{quinolone}$), 7.79 (t, 1H, *J*=7.5 Hz, H-$7_{quinolone}$), 8.26 (d, 1H, *J*=7.8 Hz, H-$5_{quinolone}$); Mass spectrum, m/z (rel. int. %): 428 [$M^{+\cdot}$] (83), 386 (100), 346 (65), 296 (77), 233 (90), 177 (87), 134 (90), 109 (48), 92 (76) and 70 (75). Anal. Calcd for $C_{24}H_{20}N_4O_4$ (428.45), C, 67.17%; H, 4.82%; N, 13.10%; found, C, 67.28%; H, 4.71%; N, 13.08%.

1-Ethyl-3-[2-(3,4,5,6-tetrahydro-3-oxopyrazin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (10).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and ethylene diamine (0.09 mL), in absolute ethanol (20 mL) containing few drops of acetic acid, was heated under reflux for 2 h. The solid obtained after cooling was filtered and crystallized from EtOH to give compound **10** as brown crystals, yield (0.21 g, 41%), m.p. > 300 °C; FT-IR (KBr) ν_{max} 3425 (OH), 3340 (NH), 3067 ($CH_{arom.}$), 2975, 2936 ($CH_{aliph.}$), 1675 ($C=O_{amide}$), 1632 ($C=O_{ketone}$ and $C=O_{quinolone}$) and 1559 cm^{-1} (C=N and C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.16 (t, 3H, CH_2CH_3), 2.70 (s, 2H, CH_2), 3.21-3.30 (m, 4H, N-CH_2-CH_2-N), 4.35 (q, 2H, CH_2CH_3), 7.16 (t, 1H, *J*=6.0 Hz, H-$6_{quinolone}$), 7.36 (d, 1H, *J*=7.2 Hz, H-$8_{quinolone}$), 7.60 (t, 1H, H-$7_{quinolone}$), 8.07 (d, 1H, *J*=7.8 Hz, H-$5_{quinolone}$), 8.70 (bs, 1H, NH exchangeable with D_2O). Mass spectrum, m/z (I_r %): 327 ($M^{+\cdot}$, 1), 246 (63), 233 (24), 216 (100), 189 (45), 172 (4), 146 (14), 132 (28), 119 (13), 91 (9), 77 (66) and 64 (50). Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.34), C, 62.31%; H, 5.31%; N, 12.89%; found, C, 62.38; H, 5.23; N, 12.84%.

1-Ethyl-3-[2-(1,2-dihydro-2-oxoquinoxalin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (11).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and o-phenylene diamine (0.16 g, 1.51 mmol) in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 2 h. The orange crystals obtained during heating were filtered and crystallized from DMF to give compound **11** as pale orange crystals, yield (0.33 g, 62%), m.p. > 300 °C; FT-IR (KBr) ν_{max} 3447 (OH), 3121 (NH), 3050 ($CH_{arom.}$), 2931 ($CH_{aliph.}$), 1685 ($C=O_{amide}$), 1647 ($C=O_{ketone}$ and $C=O_{quinolone}$), 1601 (C=N) and 1559 cm^{-1} (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (t, 3H, CH_2CH_3), 2.60 (s, 2H, CH_2), 4.24 (q, 2H, CH_2CH_3), 7.01-8.10 (m, 8H, Ar-H), 12.10 (bs, 1H, NH exchangeable with D_2O), 12.80 (bs, 1H, OH exchangeable with D_2O); Mass spectrum, m/z (rel. int. %): 375 [$M^{+\cdot}$] (10), 347 (4), 329 (3), 261 (3), 216 (6), 189 (9), 160 (15), 132 (22), 119 (6), 103 (6) and 64 (100). Anal. Calcd for $C_{21}H_{17}N_3O_4$ (375.39), C, 67.28%; H, 4.45%; N, 11.32%; found, C, 67.19%; H, 4.56%; N, 11.19%.

1-Ethyl-3-[2-(2-oxo-2H-benzo[b][1,4]-oxazin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (12).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and 2-aminophenol (0.16 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 2 h. The solid obtained during heating was filtered and crystallized from DMF to give compound **12** as orange crystals, yield (0.2 g, 37%), m.p. 260-261 ^{o}C; FT-IR (KBr) ν_{max} 3140 (OH), 3050 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 1752 ($C=O_{\alpha\text{-pyrone}}$), 1641 ($C=O_{ketone}$ and $C=O_{quinolone}$), 1604 (C=N) and 1560 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.22 (t, 3H, *J*=6.6 Hz, CH_2CH_3), 2.60 (s, 2H, CH_2), 4.26 (q, 2H, *J*=6.6 Hz, CH_2CH_3), 7.15-7.26 (m, 3H, Ar-H), 7.50 (d, 1H, *J*=8.1 Hz, Ar-H), 7.69 (d, 1H, *J*=6.9 Hz, Ar-H), 7.76 (t, 1H, *J*=7.8 Hz, Ar-H), 8.12-8.20 (m, 2H, Ar-H), 12.14 (bs, 1H, OH exchangeable with D_2O); Mass spectrum, m/z (rel. int. %): 376 [$M^{+\cdot}$] (17), 348 (21), 313 (21), 298 (23), 223 (18), 188 (21), 154 (22), 133 (100), 120 (64), 104 (89) and 77 (33). Anal. Calcd for $C_{21}H_{16}N_2O_5$ (376.37), C, 67.10%; H, 4.38%; N, 7.54%; found, C, 67.02%; H, 4.28%; N, 7.44%.

5-Ethyl-3[(1,2-dihydro-2-oxoquinoxalin-3-yl)methyl]-1H-pyrazolo[4,3-c] quinolin-4(5H)-one (13).

A mixture of compound **11** (0.50 g, 1.30 mmol) and hydrazine hydrate (0.06 mL), in absolute ethanol (20 mL), containing one drop of sulfuric acid, was heated under reflux for 10 h. The solid obtained during heating was filtered and crystallized from DMF to give compound **13** as dark orange crystals, yield (0.30 g, 61%), m.p. > 300 ^{o}C; FT-IR (KBr) ν_{max} 3196, 3129 (NH), 3040 ($CH_{arom.}$), 2975 ($CH_{aliph.}$), 1685 ($C=O_{amide}$), 1647 ($C=O_{quinolone}$), 1596 (C=N) and 1559 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.26 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 2.60 (s, 2H, CH_2), 4.28 (q, 2H, *J*=6.9 Hz, CH_2CH_3), 7.01-8.20 (m, 8H, Ar-H), 12.09 (bs, 1H, NH exchangeable with D_2O), 13.68 (bs, 1H, NH exchangeable with D_2O); Mass spectrum, m/z (rel. int. %): 370 [$M^{+\cdot}$-1] (0.4), 347 (6), 319 (2), 291 (2), 216 (24), 189 (9), 188 (14), 160 (42), 132 (100), 120 (30), 104 (15) and 64 (16). Anal. Calcd for $C_{21}H_{17}N_5O_2$ (371.40), C, 67.80%; H, 4.69%; N, 18.98%; found, C, 67.91%; H, 4.61%; N, 18.86%.

1-Ethyl-3-[2-chloro-2-(1,2-dihydro-2-oxoquinoxalin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (14).

To a suspension of compound **11** (0.50 g, 1.30 mmol) in 1,4-dioxane (30 mL), sulfuryl chloride (3 mL) was added, then the reaction mixture was stirred at room temperature for 1 h and poured onto crushed ice (*ca*. 100 g). The formed precipitate was collected by filtration and crystallized from EtOH to give compound **14** as pale yellow crystals, yield (0.38 g, 91%). m.p. 240-241 ^{o}C; FT-IR (KBr) ν_{max} 3446 (OH), 3223 (NH), 3040 ($CH_{arom.}$), 2961, 2925 ($CH_{aliph.}$), 1670 ($C=O_{amide}$ and $C=O_{ketone}$), 1636 ($C=O_{quinolone}$) and 1559 cm^{-1} (C=N and C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.26 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 4.31 (q, 2H, *J*=6.9 Hz, CH_2CH_3), 7.03 (s, H, CHCl), 7.20-7.25 (m, 2H, Ar-H), 7.31-7.37 (m, 2H, Ar-H), 7.48 (d, 1H, J=8.7 Hz, Ar-H), 7.63 (t, 1H, *J*=6.9 Hz, Ar-H), 7.79 (d, 1H, *J*=6.9 Hz, Ar-H), 8.23 (d, 1H, *J*=6.9 Hz, Ar-H), 13.69 (bs, 1H, NH exchangeable with D_2O). Mass spectrum, m/z (I_r %): 410 ($M^{+\cdot}$, 4), 375 (3), 347 (6), 305 (49), 290 (20), 277 (42), 248 (17), 213 (3), 189 (6), 172 (5), 160 (6), 144 (10), 132 (42), 118 (21), 91 (24), 77 (75) and 64 (100). Anal. Calcd for $C_{21}H_{16}ClN_3O_4$ (409.83), C, 61.50%; H, 4.00%; N, 10.44%; found, C, 61.55%; H, 3.94%; N, 10.25%.

1-Ethyl-3-[2-dibromo-2-(1,2-dihydro-2-oxoquinoxalin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (15).

A solution of bromine (0.07 mL) in acetic acid (10 mL) was added dropwise to a solution of compound **11** (0.50 g, 1.30 mmol) in acetic acid (10 mL). The reaction mixture was stirring at room temperature for 30 min. The orange crystals obtained during stirring were filtered and recrystallized from ethanol to give **15** as orange-red crystals, yield (0.30 g, 49%), mp > 300 ◦ C; FT-IR (KBr, cm^{-1}): 3445 (OH), 3201 (NH), 3090 ($CH_{arom.}$), 2923, 2853 ($CH_{aliph.}$), 1700 ($C=O_{ketone}$), 1652 ($C=O_{amide}$), 1640 ($C=O_{quinolone}$), 1615 (C=N) and 1575 (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.29 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 4.31 (q, 2H, *J*=6.9 Hz, CH_2CH_3), 7.05 (s, H, CHBr), 7.29-7.99 (m, 7H, Ar-H), 8.29 (t, 1H, *J*=8.7 Hz, Ar-H), 12.9 (bs, 1H, NH exchangeable with D_2O); Mass spectrum, m/z (rel. int. %): 454 ($M^{+\cdot}$] (5), 413 (4), 411 (4), 360 (4), 358 (5), 288 (4), 286 (4), 227 (3), 225 (4), 216 (4), 187 (10), 155 (4), 153 (4), 136 (4), 134 (4), 121 (5), 104 (7), 80 (100) and 77 (8). Anal. Calcd for $C_{21}H_{16}BrN_3O_4$ (454.28), C, 55.78%; H, 3.67%; N, 9.34%; found, C, 55.52%; H, 3.55%; N, 9.25%.

1-Ethyl-3-[2-nitro-2-(1,2-dihydro-2-oxoquinoxalin-3-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (16).

To solution of compound **11** (1.00 g, 2.60 mmol) in glacial acetic acid (10 mL), a mixture of concentrated nitric acid (2 mL) and concentrated sulfuric acid (2 mL) was carefully added portion wise with continuous stirring at room temperature for 30 min then poured onto crushed ice (*ca*. 50 gm). The solid obtained was filtered, washed with water, air-dried and crystallized from EtOH to give compound **16** as yellow crystals, yield (0.50 g, 45%), m.p. 270 ^oC. FT-IR (KBr, cm^{-1}): 3435 (OH), 3223 (NH), 2923, 2854 ($CH_{aliph.}$), 1751 ($C=O_{ketone}$), 1676 ($C=O_{amide}$), 1639 ($C=O_{quinolone}$) and 1579 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ, 300MHz): 1.22 (t, 3H, CH_2CH_3), 4.48 (q, 2H, CH_2CH_3), 7.07 (s, 1H, $CHNO_2$), 7.42-8.22 (m, 8H, Ar-H), 13.2 (bs, 1H, NH exchangeable with D_2O). Mass spectrum, m/z (I_r %): 420 ($M^{+\cdot}$, 1), 305 (1), 267 (1), 215 (2), 188 (2), 155 (3), 149 (4), 139 (5), 132 (3), 125 (11), 121 (11), 85 (36), 77 (6), 64 (30) and 57 (100). Anal. Calcd. for $C_{21}H_{16}N_4O_6$ (420.38), C, 60.00%; H, 3.84%; N, 13.33%; found, C, 60.50%; H, 4.09%; N, 13.58%.

1-Ethyl-3-[2-(2,3,4,5-tetrahydro-3-thioxo-4-amino-5-oxo-1,2,4-triazin-6-yl)acetyl]-4-hydroxyquinolin-2(1H)-one (17).

A mixture of diketoester **1** (0.50 g, 1.51 mmol) and thiocarbohydrazide (0.106 g, 1.51 mmol), in absolute ethanol (20 mL), containing few drops of acetic acid, was heated under reflux for 2 h. The orange crystals obtained during heating was filtered and crystallized from DMF to give compound **17** as pale orange crytals, yield (0.56 g, 57%), m.p. > 300 ^oC; FT-IR (KBr) v_{max} 3464 (OH), 3333 (NH), 3238 (NH_2), 2981 ($CH_{aliph.}$), 1669 ($C=O_{triazine}$), 1646 ($C=O_{ketone}$), 1621 ($C=O_{quinolone}$), 1595 (C=N) and 1563 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.20 (t, 3H, *J*=6.9 Hz, CH_2CH_3), 4.25 (q, 2H, *J*=6.9 Hz, CH_2CH_3), 4.48 (s, 2H, CH_2), 6.54 (bs, 2H, NH_2 exchangeable with D_2O), 7.34 (t, 1H, *J*=7.2 Hz, H-$6_{quinolone}$), 7.61 (d, 1H, J=8.7 Hz, H-$8_{quinolone}$), 7.80 (t, 1H, *J*=7.5 Hz, H-$7_{quinolone}$), 8.14 (d, 1H, *J*=8.1 Hz, H-$5_{quinolone}$), 12.70 (bs, 1H, NH exchangeable with D_2O), 14.00 (bs, 1H, OH exchangeable with D_2O); mass spectrum, m/z (rel. int. %): 373 [$M^{+\cdot}$] (17), 357 (11), 327 (1), 267 (2), 255 (6), 229 (7), 216 (100), 189 (8), 161 (3), 132 (14), 119 (6), 103 (5) and 64 (10). Anal. Calcd for $C_{16}H_{15}N_5O_4S$ (373.39), C, 51.50%; H, 4.19%; N, 18.68%; S, 8.65%; found, C, 51.47%; H, 4.05%; N, 18.76%; S, 8.59%.

N-{6-[2-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoethyl]-5-oxo-3-thioxo-2,5-dihydro-1,2,4-triazin-4(3H)-yl}acetamide (18).

A solution of compound **17** (0.5 g, 1.20 mmol) in acetic acid (10 mL) was heated under reflux for 4 h. The solid obtained during heating was filtered and crystallized from DMF to give compound **18** as orange crystals, yield (0.25 g, 45 %), m.p. > 300 ^{o}C; FT-IR (KBr) ν_{max} 3433 (OH), 3201 (NH), 3238 (NH_2), 2924 and 2856 ($CH_{aliph.}$), 1739 ($C=O_{acetamide}$), 1675 ($C=O_{triazine}$), 1626 ($C=O_{quinolone}$ and $C=O_{ketone}$), 1595 (C=N) and 1500 cm^{-1} (C=C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.30 (t, 3H, CH_2CH_3), 3.09 (s, 3H, CH_3), 4.59 (q, 2H, CH_2CH_3), 4.29 (s, 2H, CH2), 7.53 (t, 1H, H-$6_{quinolone}$), 7.81-7.86 (m, 2H, H-$8_{quinolone}$ and H-$7_{quinolone}$), 8.22 (d, 1H, H-$5_{quinolone}$), 8.97 (bs, 1H, NH exchangeable with D_2O), 12.7 (bs, 1H, NH exchangeable with D_2O). Mass spectrum, m/z (I_r %): 415 ($M^{+\cdot}$, 2), 389 (4), 376 (26), 332 (3), 305 (26), 277 (53), 215 (2), 189 (3), 169 (4), 132 (5), 119 (4), 101 (7) 91 (5), 77 (9) and 64 (100). Anal. Calcd for $C_{18}H_{17}N_5O_5S$ (415.42), C, 52.12%; H, 4.22%; N, 16.78%; S, 7.68%; found, C, 52.04%; H, 4.12%; N, 16.86%; S, 7.72%.

Ethyl 3-cyano-6-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-2-oxo-2H-pyran-4-carboxylate (19).

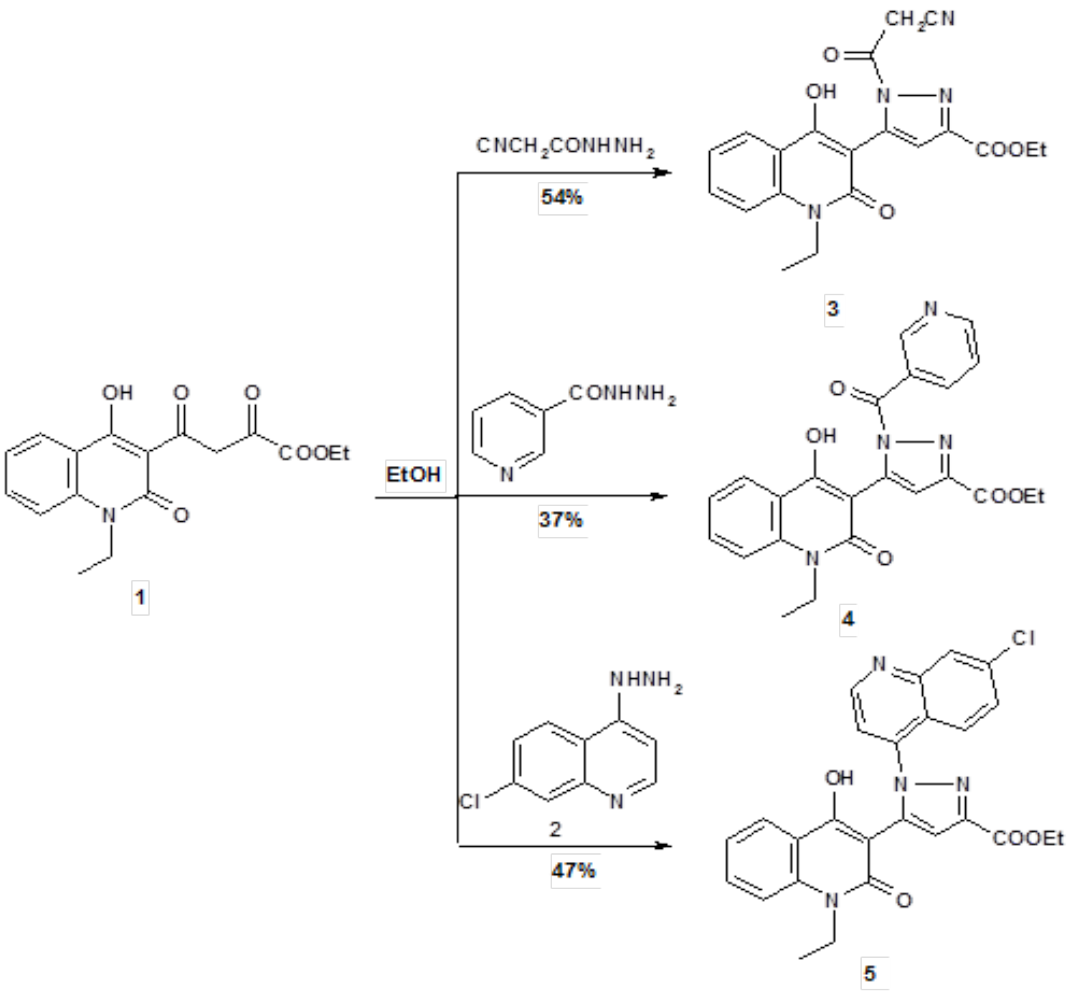
A mixture of diketoester **3** (0.50 g, 1.51 mmol) and malononitrile (0.26 g, 1.51 mmol) in ethanol (20 mL) containing few drops of TEA or acetic acid was heated under reflux for 30 min. The solid that formed during heating was filtered and crystallized from DMF to give compound **19** as pale brown crystal, yield (0.30 g, 41 %), m.p. 233-234 ^{o}C; FT-IR (KBr) ν_{max} 3445 (OH), 3265 (NH), 2985, 2922, 2843 ($CH_{aliph.}$), 2228 (C≡N), 1726 ($C=O_{ester}$), 1634 ($C=O_{quinolone}$), 1595 (C=N) and 1571 cm^{-1} (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.24 (t, 3H, *J*=6.9 Hz, N-CH_2CH_3), 1.49 (t, 3H, *J*=6.9 Hz, O-CH_2CH_3), 4.32 (q, 2H, *J*=6.9 Hz, N-CH_2CH_3), 4.49 (q, 2H, *J*=6.9 Hz, O-CH_2CH_3), 7.29 (t, 1H, *J*=7.2 Hz, H-6), 7.56 (d, 1H, *J*=8.4 Hz, H-8), 7.73 (t, 1H, *J*=8.4 Hz, H-7), 8.08 (d, 1H, *J*=8.1 Hz, H-5), 8.20 (s, 1H, H-5_{pyrane}), 9.29 (bs, 1H, NH exchangeable with D_2O), 14 (bs, 1H, OH exchangeable with D_2O).Mass spectrum, m/z (rel. int. %): 379 [$M^{+\cdot}$] (14), 365 (15), 351 (29.54), 323 (12.8), 278 (6.9), 160 (22), 146 (66.86), 132 (100), 120 (27.5), 104 (9.3) and 77 (5.35). Anal. Calcd for $C_{20}H_{17}N_3O_5$ (379.38), C, 63.20%; H, 4.61%; N, 11.00%; found, C, 63.32%; H, 4.52%; N, 11.08%.

RESULTS AND DISCUSSION

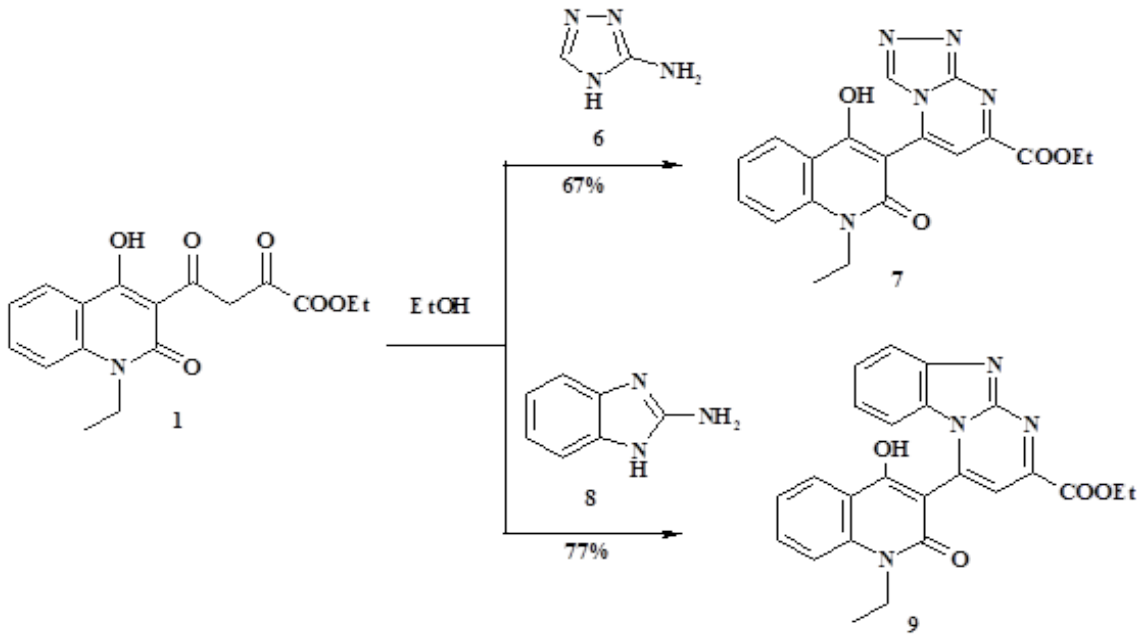
Earlier Ismail and Mohamed have reported the synthesis of ethyl 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate (**1**), in good yield [15]. The chemical behavior of this diketoester **1** was studied towards a variety of 1,2- binucleophiles, such as cyanoacetohydrazide, nicotinohydrazide and 7-chloroquinolin-4-ylhydrazine (**2**). Thus, treatment of diketoester **1** with these hydrazine derivatives, in absolute ethanol containing few drops of acetic acid, gave the corresponding pyrazole derivatives **3**-**5**, in 37-54% yields (Scheme 1). Formation of pyrazole derivatives **3-5** may occur initially via condensation of NH_2 group at ($C=O_{α\text{-keto}}$) group to give hydrazone intermediates which in turn underwent an intramolecular cyclocondensation at ($C=O_{γ\text{-keto}}$) group. The FT-IR spectra of pyrazoles **3-5** displayed characteristic absorption bands attributed to $C=O_{ester}$ at 1756, 1706, and 1707 cm^{-1}, respectively.

The FT-IR spectrum of compound **3** showed characteristic absorption bands attributed to the C≡N and $C=O_{ketone}$ at 2263 and 1695 cm^{-1}, respectively. The ^1H NMR spectra of compounds **3-5** showed characteristic signals singlet attributed to $H\text{-}4_{pyrazole}$ at δ 7.20, 7.10 and 6.40 ppm, respectively. Furthermore, the mass spectra of compounds **3**, **4** and **5** showed their molecular ion peaks at m/z 394, 432 and 489 and assigned their formula weights, respectively.

Next, the diketoester **1** was allowed to react with some 1,3-N,N-binucleophiles. Condensation of diketoester **1** with 3-amino[1,2,4]triazole (**6**), in boiling ethanol containing few drops of acetic acid, led to [1,2,4]triazolo[4,3-a]pyrimidine derivative **7** bearing the quinoline moiety (Scheme 2). The FT-IR spectrum of compound **7** showed characteristic absorption vibrations at 3447 (O-H), 1751 ($C=O_{ester}$) and 1635 cm^{-1} ($C=O_{quinoline}$). Its ^1H NMR spectrum showed two characteristic singlets at δ 8.73 ($H\text{-}5_{pyrimidine}$) and 9.40 ppm ($H\text{-}3_{triazole}$). Further, the mass spectrum of compound **7** showed the molecular ion peak at m/z 379, which is coincident with its formula weight (379.39) and supports the identity of the structure.



Scheme 1.

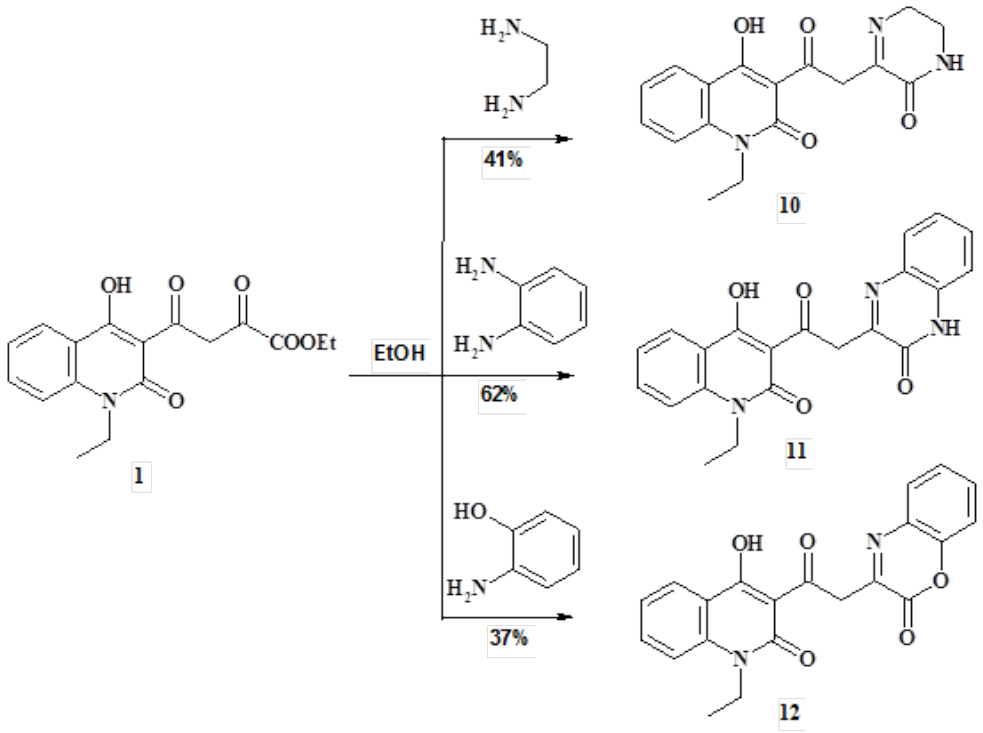


Scheme 2.

In the same manner, condensation of diketoester **1** with 2-aminobenzimidazole (**8**), in absolute ethanol containing few drops of acetic acid, produced pyrimido[1,2-*a*] benzimidazole derivative **9** linked to the quinolinone moiety (Scheme 2). The FT-IR spectrum indicated characteristic absorption vibrations at 3359 (O-H), 1707 ($C=O_{ester}$) and 1645 cm^{-1} ($C=O_{quinolone}$). The ^1H NMR spectrum of compound **9** showed characteristic singlet at δ 6.90 ($H\text{-}5_{pyrimidine}$). Further, its mass spectrum showed the molecular ion peak at m/z 370 and confirms the suggested structure.

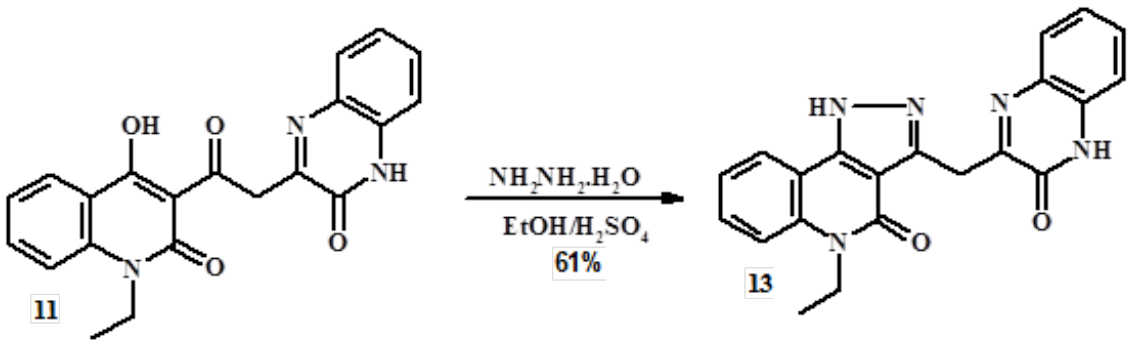
Then, the chemical reactivity of diketoester **1** was studied towards a variety of 1,4-binucleophiles. Therefore, treatment of diketoester **1** with ethylene diamine, 1,2-phenylene diamine and 2-aminophenol, in boiling ethanol containing few drops of acetic acid, furnished the corresponding pyrazine, quinoxaline and benzoxazine derivatives **10-12**, respectively (Scheme 3).

The ^1H NMR spectra of compounds **10**, **11** and **12** showed a singlet distinguishable for the active methylene protons at δ 2.70 (in compound **10**) and 2.60 ppm (in compound **11** and **12**). In addition, the FT-IR spectra of compounds **10** and **11** demonstrated stretching vibrations attributed to ($C=O_{amide}$) at 1675 and 1685 cm^{-1}, respectively, while the FT-IR spectrum of compound **12** displayed characteristic absorption band assigned to ($C=O_{\alpha\text{-}pyrone}$) group at 1752 cm^{-1}.



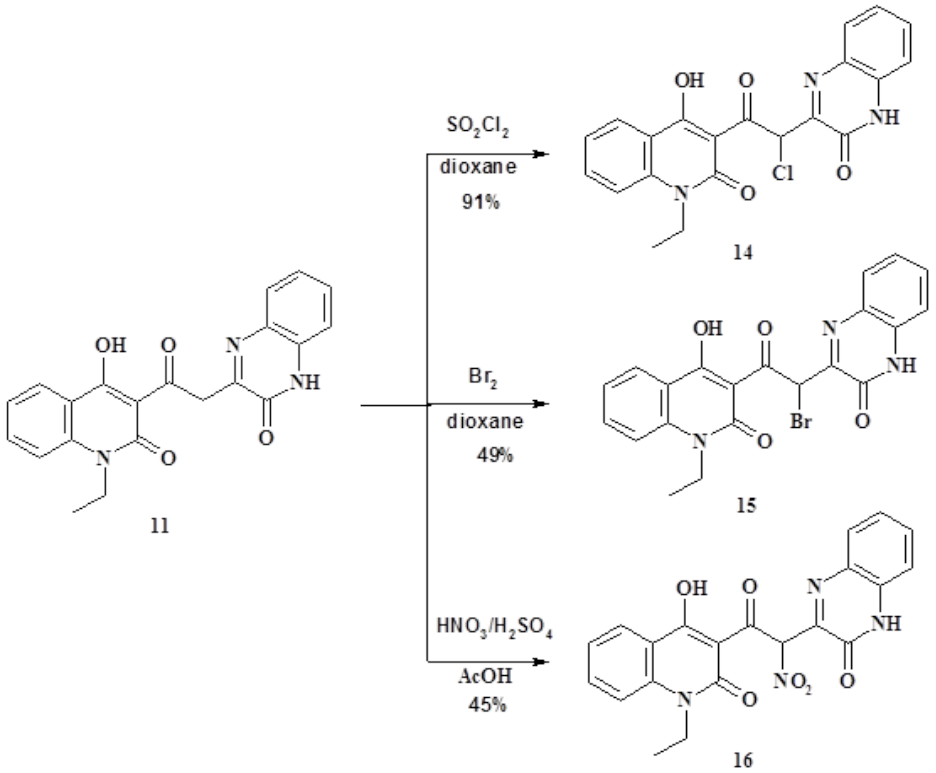
Scheme 3.

Condensation of compound **11** with hydrazine hydrate in boiling ethanol containing few drops of sulfuric acid produced pyrazolo[4,3-*c*]quinolinone **13** linked with a quinoxaline moiety in one molecular frame through an active methylene group (Scheme 4). The ^{1}H NMR spectrum of compound **13** showed a singlet distinguishable for the active methylene protons 2.60 and showed exchangeable signals at δ 12.09 and 13.68 assigned to two NH protons.



Scheme 4.

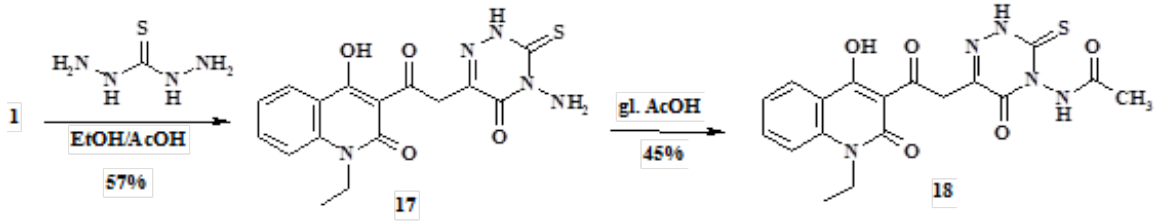
Next, the chemical reactivity of compound **11** was studied towards some electrophilic reagents. Chlorination, bromination and nitration of compound **11** afforded the chlorinated, brominated and nitrated products **14-16**, respectively (Scheme 5). The ^{1}H NMR spectra of compounds **14**, **15** and **16** showed characteristic singlets attributed to the $CH_{aliphatic}$ protons at 7.03, 7.05 and 7.07 ppm, respectively.



Scheme 5.

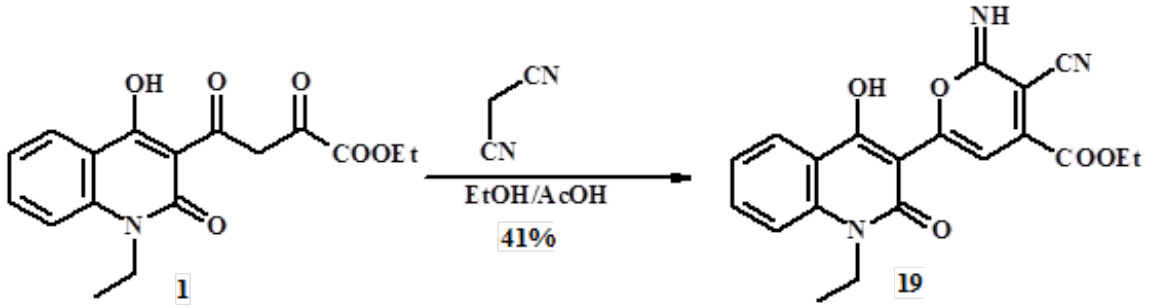
Treatment of diketoester **1** with thiocarbohydrazide, in absolute ethanol, containing few drops of acetic acid, furnished 1,2,4-triazine derivative **17** (Scheme 6). The FT-IR spectrum of compound **17** presented characteristic absorption bands at 3333, 3238 (NH, NH_2) and 1669 cm^{-1} ($C=O_{triazine}$). The ^{1}H-NMR spectrum of compound **17** showed a singlet assigned to CH_2 protons at δ 4.48, in addition to D_2O exchangeable signals at δ 6.54 and 12.70 assigned to NH_2 and NH protons, respectively.

Acetylation of compound **17** by using glacial acetic acid under reflux led to the acetylated product **18** (Scheme 6). A new absorption band appeared at 1739 cm^{-1} in the FT-IR spectrum of compound **18**, which might be assigned to ($C=O_{acetamide}$). The ^{1}H NMR spectrum of compound **18** showed exchangeable signals at δ 8.97 and 12.70 due to 2NH, respectively.



Scheme 6.

Moreover, the present work aimed to study the chemical reactivity of diketoester **1** towards malononitrile as carbon nucleophilic reagents. Thus, condensation of diketoester **1** with malononitrile, in boiling ethanol containing some drops of acetic acid, led to 3-cyano-6-(1-ethyl-1,2-dihydro-4-hydroxy-2-oxoquinolin-3-yl)-2-oxo- 2H-pyran-4-carboxylate (**19**) (Scheme 7). The FT-IR spectrum of compound **19** exhibited characteristic absorption bands at 2228 and 1726 cm^{-1} assigned to the (C≡N) and ($C=O_{ester}$), respectively. Its ^{1}H NMR spectrum indicated the presence of characteristic singlet at δ 8.20 ppm due to $H\text{-}5_{pyrane}$.



Scheme 7.

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4-(1-ETİL-1,2-DİHİDRO-4-HİDROKSİ-2-OKSOKİNOLİN-3-İL)2,4-DİOKSOBUTANOATIN BAZI NÜKLEOFİLİK REAKTİFLERE KARŞI KİMYASAL REAKTİVİTESİ

Kinolin-2-on ile bağlanmış yeni bir seri heterosiklik sistemler, etil 4-(1-etil-1,2-dihidro-4-hidroksi-2-oksokinolin-3-il)-2,4-dioksobutanoat (**1**) bileşiğinin bir seri azotlu ve/veya karbonlu nükleofillerle tepkimesinden etkili bir şekilde sentezlenmiştir. Kinolin grubu içeren pirazoller, pirimidinler, pirazinler, oksazinler ve triazinler gibi bir seri heterosiklik sistemler elde edilmiştir. Yeni sentezlenmiş ürünlerin yapıları analitik ve spektral veriler temelinde doğrulanmıştır.

Anahtar Kelimeler: Kinolin-2-on, diketoester, aktif metilen, nükleofil reaksiyon, heterohalkalaşma.

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