Scientific Journal for Damietta Faculty of Science 1 (2012) 33-41 ISSN Print 2314-8594
ISSN Online 2314-8616

Studies on 2(1*H*)-Quinolone Derivatives: Synthetic Access to Pyrano[3,2-c] Quinoline and 3-Substituted Quinoline Derivatives

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Abstract

4*H*-pyrano[3,2-*c*]quinoline derivatives 6a-f were prepared *via* reacting arylmethylenemalononitriles 2-c,g with 4-hydroxyquinolines 1a-c or 1e,f. Refluxing 6d with formic acid or acetic anhydride give 7-(2-chlorophenyl)-5-methyl-5*H*-pyrimido [5′4′:5,6]pyrano[3,2-*c*]quinoloine-6,8-(7*H*,11*H*)-dione 7 and 7-(2-chlorophenyl)-5,10-dimethyl-5*H*-pyrimido [5′4′:5,6] pyrano[3,2-*c*] quinoline-6,8-(7*H*,9*H*)-dione 9 respectively. Reacting 1d with 2a,d give pyrano[2,3-*b*] pyridine 12a,b. Compounds 1c or 1g reacted with 2e,f to give 11-amino-8-oxo-9-substituted -5,6,8,9-tetrahydro-4*H*-pyrano[3,2-*c*]pyrido[3,2,1-*ij*]quinoline-10-carbonitriles 15a,b. Reacting 1c or 1g with ethoxymethylenemalononitrile 16 afford 11-imino-4*H*,5*H*,6*H*,9*H*-benzo[*ij*][2,3-*b*]quinolizin-8-one 18. Also, reacting 1c or 1g with methyl 2-benzolyamino-3-dimethylaminopropionate 19 yield *N*-(6-(1-hydroxy-3-oxo-3,5,6,7-tetrahydropyrido[3,2,1-*ij*]quinolin-2-yl)-2-oxo-2*H*-pyran-3-yl)benzamide 21 and *N*-(8,11-dioxo-5,6,8,11-tetrahydro-4*H*-pyrano[3,2-*c*]pyrido[3,2,1-*ij*]quinolin-10-yl)benzamide 22 respectively. Condensation of 1c with aromatic aldehydes afford 2,2'-(arylmethylene)bis(1-hydroxy-6,7- dihydropyrido[3,2,1-*ij*]quinolin-3(5*H*)-ones) 28a-d.

Keywords: Arylmethylenemalononitriles, 4-Hydroxyquinolines, 4*H*-pyrano[3,2-*c*] quinoline

Introduction

4-Hydroxyquinolin-2(1*H*)-ones represents one of the most important class of heterocycles possessing wide spectrum of biological activities [1-6]. Also, they have occupied a unique place in the medicinal and biological chemistry due to their diverse pharmacological displays as antitumor [7], antimicrobial [8], antibacterial [9] and antischistosomal agents [10]. They are also useful intermediates in the manufacture of azo dyes [11].

The present work aimed at developing new synthetic routes to 4*H*-pyrano[3,2-*c*] quinoline derivatives using readily obtainable starting materials.

Materials and methods

All melting points are uncorrected and measured on Griffin and George MBF 010T (London) apparatus. Recorded yield correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrometer and ^{1}H-NMR spectra: were measured on Varian 270 MHz spectrometer on DMSO-d_6 as solvent and TMS an internal standard. Chemical shifts are reported in δ units (ppm). Microanalyses were performed on a LECO CHN-932 elemental analyzer and carried out in the Microanalytical Data Unit at Cairo and Damietta Universities. Mass spectra were recorded on a MS 30(AEI) instrument at 70 eV ionization energy.

Synthesis of pyrano[3,2-c]quinoline derivatives 6a-f:

General procedure:

Method A

A solution of 3-acetyl-4-hydroxy-2(1*H*)quinolin ones 1a,b (0.0 mole) and (0.0 mole) of α,β-unsaturated nitriles 2a-c,g in ethanol (50 ml) containing few drops of piperidine were refluxed for 15 minutes and then left to cool. The obtained precipitates were collected by filtration and recrystallised from the proper solvents and the identified as 6a-e.

Method B

Compounds 6a-e were also prepared from 4-hydroxy-2(1*H*)quinolinones 1d,e (0.01 mole) and (0.01 mole) of 2a-c,g utilizing the above reaction conditions.

2-Amino-6-ethyl-5-oxo-4-(4-phenoxyphenyl)-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile 6a:

Formed colorless crystals in 70 % yield, from n-butanol, m.p. 240-242°C; IR (ν/cm^{-1}): 3384, 3301, 3184 (NH_2), 2191 (conjugated CN), 1678 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.14-1.16 (t,j=7 Hz, 3H, CH_3), 4.18-4.20 (q,j=7 Hz, 2H, CH_2), 4.55 (s, 1H, pyran H-4), 6.83-7.62 (m, 15H, 13 H, aromatic protons and 2H, NH_2). *Anal*. Calcd. for $C_{27}H_{21}N_3O_3$ (435.47): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.67; H, 4.56; N, 9.72.

2-Amino-4-(2-chlorophenyl)-6-ethyl-5-oxo--5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile 6b:

Formed colorless crystals in 75 % yield, from n-butanol, m.p. 276-278°C; IR (ν/cm^{-1}): 3540, 3483, 3332 (NH_2), 2200 (conjugated CN), 1680 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.08-1.23 (t,j=7 Hz, 3H, CH_3), 4.18-4.20 (q,j=7 Hz, 2H, CH_2), 5.06 (s,1H,pyranH-4), 7.14-8.07 (m, 10H, 8H, aromatic protons and 2H, NH_2). *Anal*. Calcd. for $C_{21}H_{16}ClN_3O_2$ (377.82): C, 66.76; H, 4.27; N, 11.12. Found: C, 66.67; H, 4.56; N, 11.33.

2-Amino-6-ethyl-4-(2-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile 6c:

Formed colorless crystals in 80 % yield, from n-butanol, m.p. 255-257°C; IR (ν/cm^{-1}): 3540, 3483, 3332 (NH_2), 2200(conjugated CN), 1680 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.04-1.09 (t,j=7 Hz, 3H, CH_3), 4.04-4.18 (q,j=7 Hz, 2H, CH_2), 5.32 (s, 1H, pyranH-4), 7.37-8.06 (m, 10H, 8H, aromatic protons and 2H, NH_2). *Anal*. Calcd. for $C_{21}H_{16}N_4O_4$ (388.38): C, 66.94; H, 4.15; N, 14.43. Found: C, 66.91; H, 4.52; N, 14.05.

2-Amino-4-(2-chlorophenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile 6d:

Formed colorless crystals in 76 % yield, from n-butanol, m.p.290-292°C; IR (ν/cm^{-1}): 3392, 3325, 3196 (NH_2), 2200 (conjugated CN), 1678(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):3.51 (s, 3H, CH_3), 5.05 (s, 1H, pyran H-4), 7.32-8.05 (m, 10H, 8 H, aromatic protons and 2H, NH_2). *Anal*. Calcd. for $C_{20}H_{14}ClN_3O_3$ (363.80): C, 66.03; H, 3.88; N, 11.55. Found: C, 66.34; H, 4.01; N, 11.36.

2-Amino-4-(4-phenoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile 6e:

Formed colorless crystals in 76 % yield, from n-butanol, m.p. 272-274°C; IR (ν/cm^{-1}): 3412, 3315, 3192 (NH_2), 2185 (conjugated CN), 1676 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):3.30 (s, 3H, CH_3), 4.54 (s, 1H, pyranH-4), 6.90-8.00 (m, 15H, 13 H, aromatic protons and 2H,NH_2). *Anal*. Calcd. for $C_{26}H_{19}N_3O_3$ (421.45): C, 74.10; H, 4.54; N, 9.97. Found: C, 74.34; H, 4.41; N, 10.06.

Ethyl 2-amino-6-ethyl-5-oxo-4-(4-phenoxyphenyl)-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carboxylate 6f:

Formed colorless crystals in 65 % yield, from methanol, m.p. 200-202°C; IR (ν/cm^{-1}): 3390, 3286 (NH_2), 1687(CO) 1657(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.17-1.18 (t,j=7 Hz, 3H, CH_3), 1.22-1.30 (t,j=7Hz, 3H, CH_3), 4.08-4.01 (q,J=7 Hz, 2H, CH_2), 4.15-4.18 (q,j=7 Hz, 2H, CH_2), 5.12 (s, 1H, pyranH-4), 6.74 (brs, 2H,NH_2), 6.94-8.00 (m, 12H, aromatic protons). *Anal*. Calcd. for $C_{29}H_{26}N_2O_5$ (482.53): C, 72.18; H, 5.43; N, 5.81.Found: C, 72.61; H, 5.54; N, 5.52.

Formation of 7-(2-chlorophenyl)-5-methyl-5H-pyrimido [5′4′:5,6]pyrano[3,2-c]quinoloine-6,8-(7H,11H)-dione 7:

A mixture of 2-amino -4-(2-chlorophenyl) -6-methyl -5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinoline-3-carbonitrile 6d (0.01 mole) and formic acid (10 ml) was heated at reflux temperature for 10 h and then left to cool. The formed precipitate was collected by filtration and

recrystallised from n-butanol to give colorless crystals of 7, m.p. 265-267°C; IR (ν/cm^{-1}): 3533 (NH), 1773(CO), 1654(CO); *Anal*. Calcd. for $C_{21}H_{14}ClN_3O_3$ (391.81): C, 64.37; H, 3.60; N, 10.72. Found: C, 64.52; H, 3.54; N, 10.52.

Preparation of 7-(2-chlorophenyl)-5,10-dimethyl-5H-pyrimido [5'4':5,6]pyrano[3,2-c] quinoloine-6,8-(7H,9H)-dione 9:

A mixture of 2-amino -4-(2-chlorophenyl) -6-methyl -5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinoline-3-carbonitrile 6d (0.01 mole) and acetic anhydride (20 ml) was heated under reflux for 30 minutes and then left to cool. The solid product formed was collected by filtration, washed with ethanol, dried and recrystallised from DMF to give colorless crystals of 9, m.p.> 300°C; IR (ν/cm^{-1}): 3556 (NH), 1680(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):2.32(s,3H,CH_3),3.53(s,3H, *N*-CH_3), 5.32(s, 1H, pyranH-4), 7.14-8.06 (m, 8H, aromatic protons), 12.52(s, 1H,NH); *Anal*. Calcd. for $C_{22}H_{16}ClN_3O_3$ (405.83): C, 65.11; H, 3.97; N, 10.35.Found: C, 65.52; H, 3.81; N, 10.52.

Formation of 5-amino-4-aryl-2-(1-benzyl-4-hydroxy-2-oxo-1,2-dihyroquinolin-3-yl)-7-imino-7H-pyrano[2,3-b]pyridine -6-carbonitriles 12a,b

A suspension of 3-acetyl-1-benzyl-4-hydroxy-2(1*H*)quinolinone 1d (0.01 mole) in ethanol (50 ml) containing piperidine (0.1 ml) and (0.01 mole) of arylmethylenemalononitriles 1b,d was refluxed for 3h and the solids deposited upon cooling were collected by flitration, dried and recrystallised from the suitable solvents to give 12a,b

5-Amino-2-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4-(2-chlorophenyl)-7-imino-7H-pyrano[2,3-b]pyridine-6-carbonitrile
12a:Formed colorless crystals in 60 % yield, from ethanol/DMF, m.p. 280-282°C; IR (ν/cm^{-1}):3430, 3286 (NH_2,NH), 2265 (conjugated CN), 1680 (CO) 1635 (C=N). *Anal*. Calcd. for $C_{31}H_{20}ClN_5O_3$ (545.98): C, 68.20; H, 3.96; N, 12.83. Found: C, 72.61; H, 5.54; N, 5.52.

5-Amino-2-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4-(4-hydroxyphenyl)-7-imino-7H-pyrano[2,3-b]pyridine-6-carbonitrile
12b: Formed colorless crystals in 65 % yield, from methanol/DMF, m.p. 200-202°C; IR (ν/cm^{-1}): 3464, 3312 (NH_2, NH), 2200 (conjugated CN), 1680 (CO) 1627 (C=N); ^{1}H-NMR (DMSO-d_6)(δ,ppm): 4.52 (s, 1H, NH), 5.41, 5.51(2d,j=15.6 Hz, 2H, N-CH_2), 6.67 (d,j=7.5 Hz, 2H, aromatic protons), 7.03-7.62 (m,15H, aromatic protons),8.08 (d,j=7.5 Hz,1H quinoline H-8) 9.32 (s, 2H, NH_2), 10.10 (s, 1H, OH). *Anal*. Calcd. for $C_{31}H_{21}N_5O_4$ (527.53): C, 70.58; H, 4.01; N, 13.28. Found: C, 70.53; H, 4.34; N, 13.42; MS:M^+ = 527 (m/z).

Preparation of 11-amino-8-oxo-9-substituted-5,6,8,9-tetrahydro-4H-pyrano[3,2-c]pyrido[3,2,1-ij]quinoline-10-carbonitriles 15a,b

Method A:

Equimolecular amounts of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)–one 1c (0.01mole), formaldehyde or acetaldehyde (0.01mole) and malononitrile (0.01mole) in ethanol (50 ml) were treated with (0.1 ml) piperidine. The reaction mixture was refluxed for 2h.and then cooled to room temperature. The solid products formed were collected by filtration and recrystallised from suitable solvents to give 15a,b.

Method B:

Compounds 15a,b were also prepared by refluxing 1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1g (0.01 mole), formaldehyde or acetaldehyde (0.01mole) and malononitrile (0.01mole) in ethanol (50 ml), containing few drops of piperidine. The reaction mixture was refluxed for 2h and then cooled to room temperature. The solid products obtained were collected by filtration and recrystallised from suitable solvents and then identified (m.p., mixed m.p. and IR) as 15a,b.

11-Amino-8-oxo-5,6,8,9-tetrahydro-4H-pyrano[3,2-c]pyrido[3,2,1-ij]quinoline-10-carbonitrile 15a: Formed colorless crystals in 60 % yield, from methanol/DMF, m.p. > 300°C; IR (ν/cm^{-1}):3323,3267 (NH_2),2192(conjugated CN), 1680(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.96 (m, 2H, CH_2), 2.92(t,j=6 Hz, 2H, Ar-CH_2), 4.04(t,j=6 Hz, *N*-CH_2), 7.11 (s, 2H, NH_2), 7.12 (t,j=7 Hz, 1H, quinolizine H-9), 7.43 (d,j=7Hz, 1H, quinolizine H-8), 7.7 (d,j=7 Hz, 1H, quinolizine H-10). *Anal*. Calcd. for $C_{16}H_{13}N_3O_2$ (279.29): C, 68.81; H, 4.69; N, 15.05. Found: C, 68.66; H, 4.54; N, 15.32.

11-Amino-9-methyl-8-oxo-5,6,8,9-tetrahydro-4H-pyrano[3,2-c]pyrido[3,2,1-ij]quinoline-10-carbonitrile 15b: Formed colorless crystals in 60 % yield, from ethanol/DMF, m.p. 290 - 292^{o}C; IR (ν/cm^{-1}): 3389, 3323 (NH_2), 2190 (conjugated CN), 1673(CO). *Anal*. Calcd. for $C_{17}H_{15}N_3O_2$ (293.12): C, 69.61; H, 5.15; N, 14.33. Found: C, 68.66; H, 4.54; N, 15.32.

11-Imino-4H,5H,6H,9H-benzo[ij][2,3-b]quinolizin-8-one 18

A solution of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)–one 1c (0.01mole) in ethanol (50 ml) containing piperidine (0.01 ml) was treated with ethoxymethylenemalononitrile 16 (0.01mole). The reaction mixture was heated under reflux for 6h.The solvent was concentrated to its half volume and the mixture left to cool. The precipitates formed was collected by filtration and recrystallised from ethanol to give 18 as colorless crystals in 60 % yield, m.p.195-197^{o}C; IR (ν/cm^{-1}): 3425 (NH_2), 2213(conjugated CN), 1673(CO). *Anal*. Calcd. for $C_{16}H_{11}N_3O_2$ (277.28): C, 69.31; H, 4.00; N, 15.15. Found: C, 69.46; H, 4.34; N, 15.21.

11-Imino-4*H*,5*H*,6*H*,9*H*-benzo[*ij*][2,3-*b*]quinolizin-8-one 18 was also prepared by reacting equimolar amounts of 1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1g and ethoxymethylenemalononitrile 16 using the same reaction conditions.

Preparation of N-(6-(1-hydroxy-3-oxo-3,5,6,7-tetrahydropyrido[3,2,1-ij]quinolin-2-yl)-2-oxo-2H-pyran-3-yl)benzamide 21

A suspension of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1c (0.01mole) and methyl 2-benzolyamino-3-dimethylaminopropionate 19(0.01mole) in acetic acid (20 ml) was heated under reflux for 5h. The reaction mixture was cooled at room temperature and the solid formed was collected by filtration, washed with ethanol, then recrystallised from acetic acid to give 21 as pale yellow crystals in 65 % yield m.p. > 300^{o}C; IR (ν/cm^{-1}): 3422 (NH), 1680 (CO) 1627 (C=O). *Anal*. Calcd. for $C_{24}H_{18}N_2O_5$ (414.41): C, 69.56; H, 4.38; N, 6.76. Found: C, 69.43; H, 4.45; N, 6.82; MS: M^+ = 415 (m/z).

Formation of N-(8,11-dioxo-5,6,8,11-tetrahydro-4H-pyrano[3,2-c]pyrido[3,2,1-ij]quinolin-10-yl)benzamide 22

A suspension of 1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1g (0.01mole) and methyl 2-benzolyamino-3-dimethylaminopropionate 19 (0.01mole) in acetic acid (20 ml) was heated under reflux for 3h. The solvent was evaporated under reduced pressure, triturated with methanol and then left to cool at room temperature and the solid formed was collected by filtration, washed with ethanol, then recrystallised from acetic acid to give 22 as yellow crystals in 60 % yield m.p. > 300^{o}C; IR (ν/cm^{-1}): 3253 (NH), 1724 (CO), 1668 (CO). *Anal*. Calcd. for $C_{22}H_{16}N_2O_4$ (372.37): C, 70.96; H, 4.33; N, 7.52. Found: C, 70.85; H, 4.45; N, 7.82.

Formation of 2,2'-(arylmethylene)bis(1-hydroxy-6,7- dihydropyrido[3,2,1-ij]quinolin-3(5H)-ones) 28a-c

A suspension of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1c (0.01mole) in ethanol (50 ml) was treated with the appropriate amount of aromatic aldehydes and few drops of piperidine. The reaction mixture was refluxed for 3h and the solids deposited upon heating was collected by filtration, recrystallised from the proper solvents and then identified as 28a-c.

2,2'-(Phenylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-ij]quinolin-3(5H)-one) 28a: Formed colorless crystals in 60 % yield, from ethanol, m.p. 196-198^{o}C; IR (ν/cm^{-1}): 3450-3384 (OH), 1628(CO). *Anal*. Calcd. for $C_{31}H_{26}N_2O_4$ (490.55): C, 75.90; H, 5.34; N, 5.71. Found: C, 76.12; H, 5.17; N, 5.42.

2,2'-((4-Hydroxyphenylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-ij] quinolin-3(5H)-one) 28b:

Formed colorless crystals in 60 % yield, from methanol/DMF, m.p. 284-286^{o}C; IR (ν/cm^{-1}): 3437 (OH), 1622(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm): 2.49 (m, 2H,CH_2), 2.95 (t,j=6Hz, 2H, Ar-CH_2), 4.10 (t,j=6 Hz, *N*-CH_2),6.15 (s, 1H CH), 7.12 (t,j=7 Hz, 1H, quinolizine H-9), 7.43 (d,j=7 Hz, 1H, quinolizine H-8), 7.7 (d,j=7 Hz, 1H, quinolizine H-10), 9.17(s, 1H, OH). *Anal*. Calcd. for $C_{31}H_{26}N_2O_5$ (506.18): C, 73.50; H, 5.17; N, 5. 53. Found: C, 73.66; H, 5.34; N, 5.32; MS: M^+ = 506 (m/z).

2,2'-((4-Chlorophenylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-ij] quinolin-3(5H)-one) 28c: Formed colorless crystals in 60 % yield,

from ethanol/DMF, m.p. 245-247°C; IR (ν/cm^{-1}): 3422 (OH), 1607 (CO). *Anal*. Calcd. for $C_{31}H_{25}ClN_2O_4$ (524.99): C, 70.92; H, 4.80; N, 5.34. Found: C, 70.48; H, 4.54; N, 5.22.

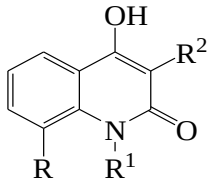
2,2'-((4-Bromophenylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-ij] quinolin-3(5H)-one) 28d:
Formed colorless crystals in 60 % yield, from ethanol/DMF, m.p.230-232°C; IR (ν/cm^{-1}): 3449 (OH), 1624(CO). *Anal*. Calcd. for $C_{31}H_{25}BrN_2O_4$ (569.45): C, 65.38; H, 4.43; N, 4.92. Found: C, 65.48; H, 4.54; N, 5.02.

Results and Discussion

As a part of our program directed for developing simple and efficient procedures for synthesis of functionally substituted pi-deficient heterocycles as biodegradable agrochemicals and antischistosomal agents [12-14]. We report here new access for synthesis of several new 2(1*H*)-quinolone derivatives by reacting 4-hydroxyquinolin-2(1*H*)-one derivatives 1a-g with different reagents. Also, in this work, the nature of the end products was found to be dependent on the nature of the utilized reactants.

It has been found that, 3-acetyl-4-hydroxy-2(1*H*)quinolinones 1a,b reacted with arylmethylenenitriles 2a-c,g in ethanol and in the presence of catalytic amounts of piperidine, was thought to afford two products, 2-amino-4-aryl-6-(4-hydroxy-2-oxo-1,2-dihydroquinolin-yl)-3-substituuted -4*H*-pyran derivatives 3 and 2-amino-4-aryl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline derivatives 6 (Fig. 1 and 2). Structures 3 were readily ruled out by analytical and spectral data of the reaction products.

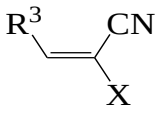
Thus, structures 6 were established for the reaction products based on ^{1}H-NMR spectra which revealed the presence of pyran-4*H* protons at δ = 4.5-5.0 ppm. Compounds 6 were assumed to be formed *via* addition of quinolinyl C-3 to the π-deficient center in 2 to give the adduct 4, which hyrolysed and readily eliminate its acetyl group under the reaction conditions to give the intermediates 5. These were cyclised to 6. Elimination of the acetyl groups in this reactions parallels the reported deacetylation of similar systems under similar conditions [12-14]. Compounds 1 may be existing as 4-quinolone [12-14], at which quinolin-3-position becomes more acidic than its acetyl group. Moreover, the steric effect in the intermediates 4 facilitates deacetylation process. The structures of compounds 6 were also confirmed by synthesizing them from reaction of 4-hydroxy-2(1*H*)-quinolones 1d,e under the same reaction conditions(*cf.* Scheme 1).



1

1	R	R^1	R^2
a	H	C_2H_5	$COCH_3$
b	H	CH_3	$COCH_3$
c	- $(CH_2)_3$ -		$COCH_3$
d	H	CH_2Ph	$COCH_3$
e	H	C_2H_5	H
f	H	CH_3	H
g	- $(CH_2)_3$ -		H

Fig. 1 4-Hydroxyquinolines



2

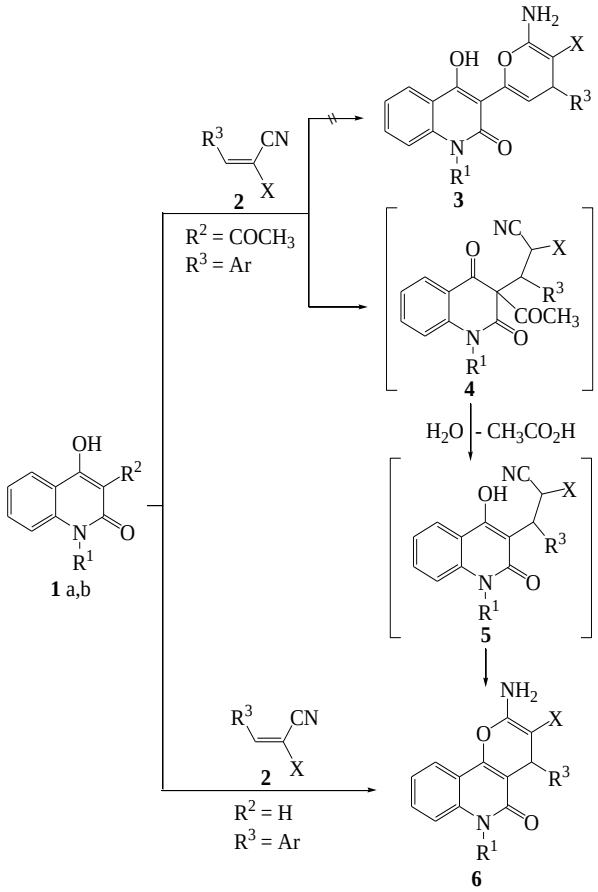
2	R^3	X
a	$C_6H_4OPh(m)$	CN
b	$C_6H_4Cl(o)$	CN
c	$C_6H_4NO_2(o)$	CN
d	$C_6H_4OH(p)$	CN
e	H	CN
f	CH_3	CN
g	$C_6H_4OPh(m)$	$CO_2C_2H_5$

Fig. 2 4- Arylmethylenenitriles

2-Amino -4-(2-chlorophenyl) -6-methyl -5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinoline-3-carbonitrile 6d as a typical enaminonitrile derivative reacted with formic acid for few hours to yield 7-(2-chlorophenyl)-5-methyl-5*H*-pyrimido [5'4':5,6]pyrano[3,2-*c*]quinoloine-6,8-(7*H*,11*H*)-dione 7.

Compound 6d also reacted with acetic anhydride to give *N*-(4-(2-chlorophenyl)-3-cyano-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinolin-2-yl)acetamide 8 or 7-(2-chlorophenyl)-5,10-dimethyl-5*H*-pyrimido [5'4':5,6]pyrano[3,2-*c*] quinoloine-6,8-(7*H*,9*H*)-

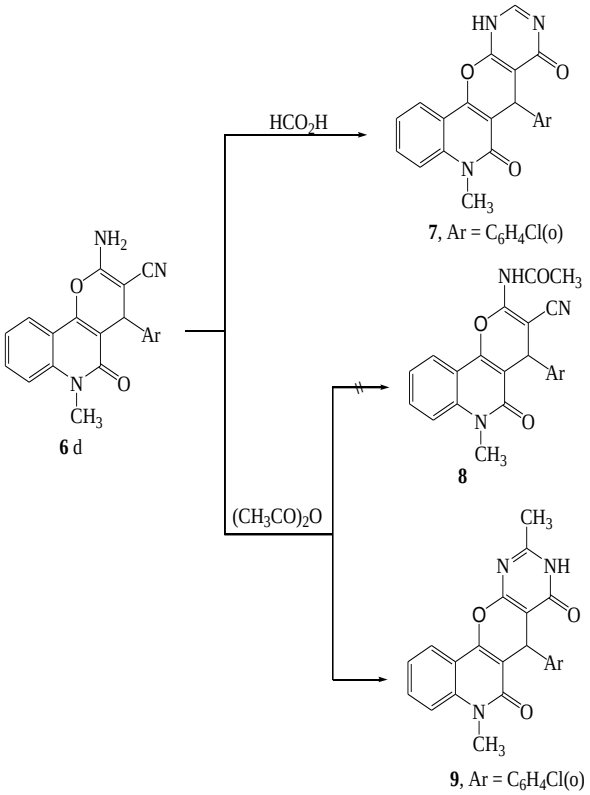
dione 9.Structure 8 was readily ruled out based on IR spectrum which clearly indicates the absence of cyano group. Thus, Structure 9 was established as a reaction product (*cf.* Scheme 2).



6	R^1	R^3	X
a	C_2H_5	C_6H_4OPh(m)	CN
b	C_2H_5	C_6H_4Cl(o)	CN
c	C_2H_5	$C_6H_4NO_2$(o)	CN
d	CH_3	C_6H_4Cl(o)	CN
e	CH_3	C_6H_4OPh(m)	CN
f	C_2H_5	C_6H_4OPh(m)	$CO_2C_2H_5$

Scheme 1 Synthesis of 4*H*-pyrano[3,2-*c*]quinolines 6a-e.

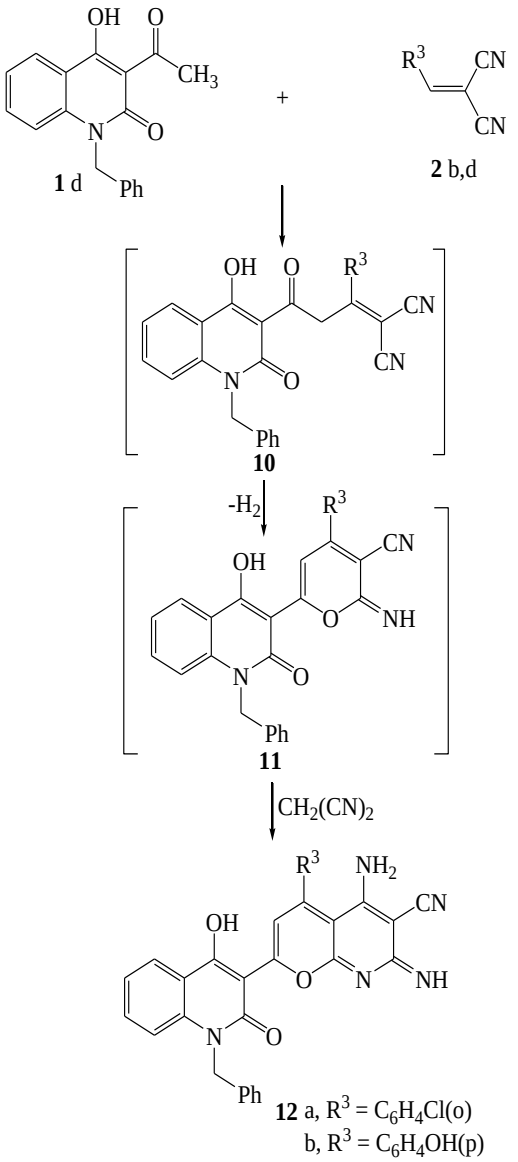
In contrast to the behavior of 3-acetyl-4-hydroxy-2(1*H*)quinolinones 1a,b towards arylmethylenemalononitriles 2a-c, 3-acetyl-1-benzyl-4-hydroxy-2(1*H*)quinolinone 1d reacted with arylmethylenemalononitriles 2b,d in ethanol/piperidine in a molar ratio (1:1) or (1:2) to yield 5-amino-4-aryl-2-(1-benzyl-4-hydroxy-2-oxo-1,2-dihyroquinolin-3-yl)-7-imino-7*H*-pyrano[2,3-*b*]pyridine -6-carbonitriles 12a,b. Elemental analyses and spectral data are in full agreement with the proposed structures 12a,b (*cf.* Experimental). Compounds 12a,b were likely formed *via* Michael type addition of the enolate ion of the acetyl group in 3-acetyl-1-benzyl-4-hydroxy-2(1*H*)quinolinone 1d to activated double bond in 2a,d to give the acyclic adducts 10, which then dehydrogenated and cyclized into the intermediates 11. The intermediates 11 then add one molecule of malononitrile, which exists in equilibrium with 2 especially under basic conditions [13] (*cf.* Scheme 3).



Scheme **2**: Reaction of **6d** with formic acid and acetic anhydride.

11-Amino-8-oxo-9-substituted-5,6,8,9-tetrahydro-4*H*-pyrano[3,2-*c*]pyrido[3,2,1-*ij*] quinoline-10-carbonitriles 15a,b prepared *via* reacting 2-acetyl-1-hydroxy-6,7-dihydropyrido [3,2,1-*ij*] quinolin-3(5*H*) -one 1c with a mixture of formaldehyde or acetaldehyde with malononitrile. Structures of compounds 15a,b were assigned for these reaction products on the basis of their identity with the products of reaction of 1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*). 1f with formaldehyde or acetaldehyde/malononitrile mixture. It is suggested that compounds 15a,b were formed *via* addition of quinolinylC-3 in 1c to the double bond in 2e,f (formed in *situ* by treating formaldehyde or acetaldehyde with malononitrile) to give the adducts 13 which deacetylated to give the intermediates 14 and

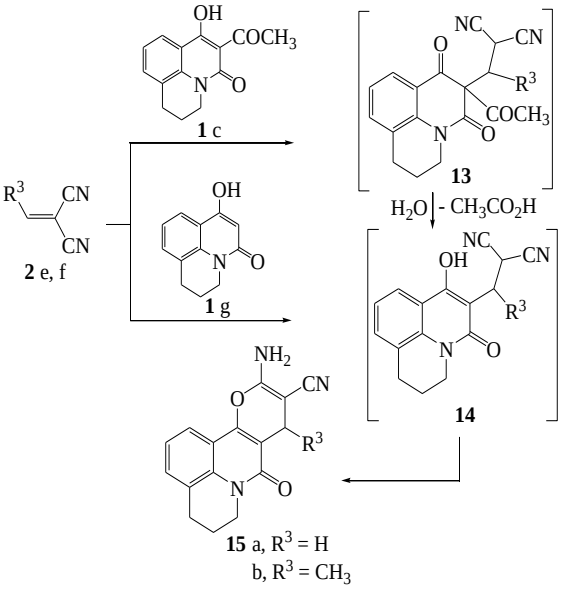
then cyclised to compounds 15a,b (*cf.* Scheme 3).



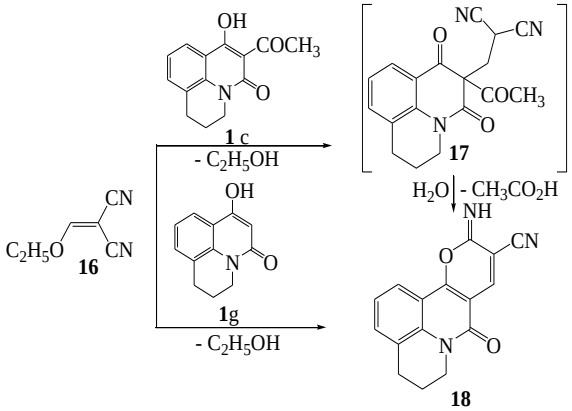
Scheme **3**:Formation of pyrano[2,3-b]pyridines **12a,b**.

Also, refluxing of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1c ethoxymethylenemalononitrile 16 in absolute ethanol containing catalytic amounts of piperidine resulted in the formation of 11-imino-4*H*,5*H*,6*H*,9*H*-benzo[*ij*][2,3-*b*]quinolizin-8-one 18. Elemental analysis and IR spectrum are in good agreement with structure 18. The same product 18 also obtained by reacting ethoxymethylenemalononitrile 16 with 1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1g utilizing the same reaction conditions (*cf.* Scheme 5).

We have also studied the reactivity of 2-acetyl-1-hydroxy-6,7-dihydropyrido [3,2,1-*ij*] quinolin-3(5*H*)-one 1c towards enaminoesters and aromatic aldehydes. Thus, compound 1c reacted with methyl 2-benzolyamino-3-dimethylaminopropionate 19 in refluxing acetic acid to afford *N*-(6-(1-hydroxy-3-oxo-3,5,6,7-tetrahydropyrido[3,2,1-*ij*]quinolin-2-yl)-2-oxo-2*H*-pyran-3-yl)benzamide 21. Structure 21 was supported by elemental analysis and spectral data. Compound 21 was proposed to be formed by first condensation of quinolinyl C-3 with 19 to give the intermediate 20 and then cyclised through methanol elimination to yield 21 (*cf.* Scheme 6).



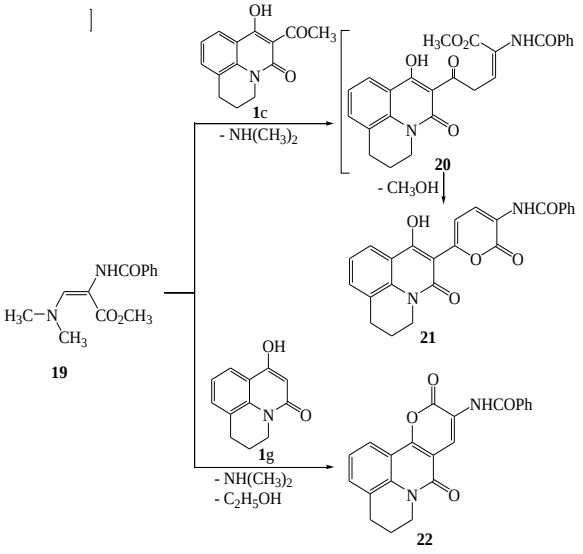
Scheme **4**: Synthesis of pyranoquinolines **15a,b**.



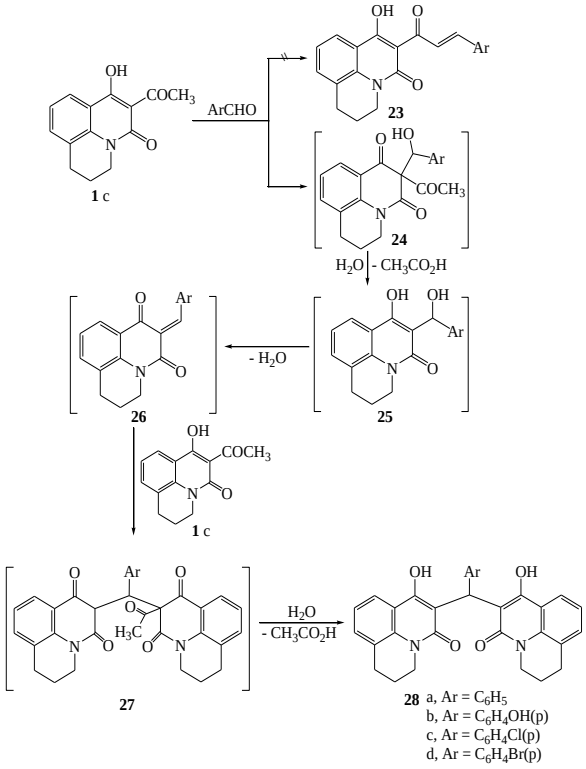
Scheme **5**: Synthesis of pyrano quinolines **18**.

On the other hand, cyclocondensation of 1-hydroxy-6,7-dihydropyrido [3,2,1-*ij*] quinolin-3(5*H*)-one 1g with methyl 2-benzolyamino-3-dimethylaminopropionate 19 in refluxing acetic acid resulted in the formation of *N*-(8,11-dioxo-5,6,8,11-tetrahydro-4*H*-pyrano[3,2-

c]pyrido[3,2,1-*ij*]quinolin-10-yl)benzamide 22 *via* dimethylamine and methanol elimination (*cf.* Scheme 6).



Scheme **6**: Reaction of enaminesters **19** with **1c** and **1f**.



Scheme **7**: Reaction of **1c** with aromatic aldehydes.

In addition, 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one 1c condensed with aromatic aldehydes in a molar ratio (1:1) or (1:2), performed in ethanol and in presence of piperidine as catalyst, for which two products, (*E*)-2-(3-arylacryloyl)-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*]quinolin-3(5*H*)-ones) 23 and 2,2'-(arylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*]quinolin-3(5*H*)-ones) 28 seemed possible. Structures 23 were readily eliminated by analytical data and mass spectra of the reaction products. Therefore, structures 28a-d were established for the reaction products. Also, ^{1H}-NMR-spectrum showed the presence of signal δ = 6.15 ppm for CH group. 2,2'-(arylmethylene)bis(1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*]quinolin-3(5*H*)-ones) 28a-d were thought to be obtained (*cf.* Scheme 7).

Conclusion

We conclude that, several new 4*H*-pyrano[3,2-*c*] quinolines and 3-substituted quinolines were prepared *via* reacting 4*H*-hydroxyquinolines with arylmethylenenitiles as readily obtainable starting materials that could be useful for biological evaluation studies.

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الملخص العربى

دراسات على مشتقات 4-هيدروكسى كينولين: طرق جديدة لتحضير مشتقات البيرانوكينولين

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من المعروف أن مشتقات الكينولين تستخدم كمواد أولية جيدة لتحضير مجموعات من المركبات التى لها جانب تطبيقى فى الكيمياء العلاجية. ومن هنا اتجهنا فى هذا البحث الى تحضير مشتقات جديدة من البيرانوكينولين من 4-هيدروكسى كينولين والأريل ميثيلين نيتريلات كمواد أولية سهلة التحضير. ومن المتوقع أن يكون لهذه المركبات نشاط بيولوجى جيد. وتم إثبات التركيب البنائى للمركبات الناتجة باستخدام طرق التحليل الطيفي والعنصرى.