Studies on quinolin-2(1*H*)-one 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 gave 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*] quinoloine-6,8-(7*H*,9*H*)-dione **9** respectively.Reacting **1d** with **2a,d** gave 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** afforded 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

1.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 dyestuffs,that can be used for dyeing both naturally occurring and synthetic fibres [11].

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 agants [12-14]. We report here new access for synthesis of several new pyrano[3,2-*c*]quinoline and 3-substituted quinoline 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 were found to be dependent on the nature of the utilized reactants .

2.Experimental

All melting points are uncorrected and measured on Griffin 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-hydroxyquinolin-2(1*H*)-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:

Copmounds **6a-e** were also prepared from 4-hydroxyquinolin-2(1*H*)-ones **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**:Colorless needles (3.5g ,70) , from n-butanol , m.p.240-242^{o}C ; IR (ν/cm^{-1}): 3384,3301,3184(NH_2),2191(CN),1678(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.15 (t,J = 7.5Hz,3H,CH_3) ,4.19 (q,J=7.5Hz, 2H, CH_2) , 4.55(s,1H ,pyran H-4), 6.83-7.12 (m, 13 H,aromatic protons) ,7.65(s, 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; MS : M^+ = 435(m/z).

2-Amino-4-(2-chlorophenyl)-6-ethyl-5-oxo--5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile **6b** : Colorless needles (2.8g , 75 %) , from n-butanol ,m.p.276-278^{o}C ; IR (ν /cm^{-1}): 3540, 3483,3332 (NH_2),2200 (CN) , 1680(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):1.16 (t,J = 7.5Hz,3H,CH_3) , 4.20(q,J = 7.5Hz, 2H, CH_2) , 5.06(s,1H,pyranH-4), 7.14-7.76 (m, 8 H,aromatic protons) 8.17(s, 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; MS : M^+ = 377(m/z).

2-Amino-6-ethyl-4-(2-nitrophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carbonitrile **6c** : Colorless needles (2.8 g,80 %) , from n-butanol ,m.p.255-257^{o}C ; IR (ν /cm^{-1}): 3540,3483,3332(NH_2) ,2200(CN) , 1680 (CO); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :1.06 (t,J = 7.5Hz,3H,CH_3) ,4.20 (q,J = 7.5Hz ,2H , CH_2), 5.32 (s,1H, pyranH-4),7.65-7.78 (m, 8 H,aromatic protons), 8.06(s, 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** : Colorless needles (2.5 g, 76 %) , from n-butanol ,m.p.290-292^{o}C ; IR (ν /cm^{-1}): 3392,3325,3196 (NH_2), 2200 (CN), 1678 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):3.51 (s, 3H,CH_3),5.05(s,1H,pyranH-4),7.32-7.77 (m, 8 H,aromatic protons),(8.11(s, 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** : Colorless needles (3g, 70 %) , from n-butanol ,m.p.272-274^{o}C ; IR (ν /cm^{-1}): 3412,3315,3192(NH_2), 2185 (CN), 1676 (CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm):3.30 (s, 3H,CH_3),4.54(s,1H,pyranH-4),6.90-7.78 (m, 13 H,aromatic protons),8.00(s, 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; MS : M^+ = 421(m/z).

Ethyl 2-amino-6-ethyl-5-oxo-4-(4-phenoxyphenyl)-5,6-dihydro-4H-pyrano[3,2-c] quinoline-3-carboxylate **6f**: Colorless needles (2.9g,60 %) , from methanol ,m.p.200-202^{o}C ; IR (ν /cm^{-1}): 3390,3286 (NH_2), 1687(CO) 1657(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm): 1.18 (t,J=7.5Hz,3H,CH_3) , 1.25 (t, J= 7.5Hz , 3H,CH_3) ,4.05 (q,J=7.5Hz,2H,CH_2), 4.17(q,J=7.5Hz,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; MS : M^+ = 482(m/z).

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** (3.63g ,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 needles of **7**(2.3g,60%) , m.p.265-267^{o}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 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** (3.63g,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 needles of **9** (2.4g,60%), m.p.> 300^{o}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-hydroxyquinolinon-2(1*H*)-one **1d** (2.93g , 0.01 mole) in ethanol (50 mL) containing piperidine (0.1mL) and (0.01 mole) of arylmethylenemalononitriles **1b,d** was refluxed for 3h and the solids deposited upon cooling were collected by filtration , 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** : Colorless needles (3.3g, 60 %) , from ethanol / DMF,m.p.280-282^{o}C ; IR (ν /cm^{-1}) :3430 , 3286(NH_2,NH),2265(CN),1680(CO),1635(C=N), ^{1}H-NMR (DMSO-d_6)(δ,ppm) :4.95(s,2H,*N*-CH_2),7.23-8.11(m,14H,aromatic protons),8.66(s,2H,NH_2), ^{13}C-NMR (DMSO-d_6)(δ,ppm) :48.9 ,73.6,105.4, 115.4,115,7,115,7,115.9, 120.8, 123.9, 124.4,126.6,126.8,127.8,128.6,129.4,131.2,136.2,140.5,158.3,160.4,164.6,182.8

.Anal. Calcd.for $C_{31}H_{20}ClN_5O$ (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** : Colorless needles (1.4g, 65 %) , from methanol / DMF ,m.p.200-202^oC ; IR (ν / cm^{-1}): 3464 ,3312 (NH_2 , NH),2200(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** (2.43g,0.01mole) ,formaldehyde or acetaldehyde (0.01mole) and malononitrile (0.66g,0.01mole) in ethanol (50mL) were treated with (0.1mL) 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-dihydro pyrido[3,2,1-*ij*]quinolin-3(5*H*)-one **1g**[16] (2.01g,0.01mole) ,formaldehyde or acetaldehyde (0.01mole) and malononitrile (0.66g,0.01mole) in ethanol (50mL), 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** : Colorless needles (1.7g, 60 %) , from methanol / DMF ,m.p. > 300^oC ; IR (ν /cm^{-1}): 3323,3267 (NH_2),2192(CN), 1680(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm): 1.96 (m , 2H ,CH_2),2.92(t,J = 6.5Hz,2H ,Ar-CH_2) ,4.04(t, J = 6.5Hz ,*N*-CH_2),7.11(s, 2H , NH_2), 7.12(t,J = 7.5Hz ,1H,quinolizine H-9), 7.43 (d,J = 7.5 Hz ,1H,quinolizine H-8),7.7(d,J = 7.5Hz ,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** : Colorless needles (1.6g, 60 %) , from ethanol / DMF ,m.p. 290 - 292^oC ; IR (ν /cm^{-1}): 3389,3323 (NH_2),2190(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** (2.43g,0.01mole) in ethanol (50mL) containing piperidine (0.01mL) was treated with ethoxymethylenemalononitrile **16** (1.22g,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 needles (2g, 60 %),m.p.195-197^oC ; IR (ν /cm^{-1}): 3425 (NH_2),2213(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**(16)(2.01g) and ethoxymethylenemalononitrile **16**(1.22g) using the above mentioned 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** (2.43g,0.01mole) and methyl 2-benzolyamino-3-dimethylaminopropionate **19**(2.48g,0.01mole) in acetic acid (20mL) 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 plates (2.7g, 65 %), m.p. > 300^oC; IR (ν /cm^{-1}): 3422 (NH), 1680 (CO) 1627(C=O), ^{1}H-NMR (DMSO-d_6)(δ,ppm): 1.9,(m,J=6.5Hz ,2H, CH_2) , 2.76 (t,J=6.5Hz),3.18(t,J=6Hz,1H,*N*-CH_2),6.45 (d,J=6Hz,1H) ,6.99 (d ,J= 6.5Hz, 1H),7.15-7.97(m,8H,aromatic protons),8.0 (s,1H,NH). *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** [16] (2.01g,0.01mole) and methyl 2-benzolyamino-3-dimethylaminopropionate **19**(2.48g,0.01mole) in acetic acid (20mL) 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 plates (2.2g, 60 %), m.p. > 300^{o}C; IR (ν /cm^{-1}): 3253 (NH), 1724 (CO), 1668 (CO), ^{1}H-NMR (DMSO-d_6)(δ,ppm) :1.84(m,J=6.5Hz,2H,CH_2), 2.76 (t,J= 6.5Hz, 2H, CH_2), 3.18(t,J=6.5Hz,*N*-CH_2),.95-7.93(m,9H,aromatic protons), 8.1(s,1H,NH). *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** (2.43g,0.01mole) in ethanol (50mL) was treated with (0.01mole) 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** : Colorless needles (2.9g,60 %),from ethanol,m.p. 196-198^{o}C ; IR (ν /cm^{-1}): 3450-3384 (OH), 1628(CO), ^{1}H-NMR (DMSO-d_6) (δ,ppm): 2.44 (m , 2H ,CH_2),2.85(t, J = 6Hz ,2H , Ar-CH_2) ,3.90(t, J = 6Hz ,*N*-CH_2),6.17(s, 1H CH), 7.12(t,J = 7Hz ,1H,quinolizine H-9), 7.43 (d,J = 7Hz , ,1H,quinolizine H-8),7.73 (d,J = 7Hz ,1H, quinolizine H-10), 16.75(s,1H,OH). *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** : Colorless needles (3g,60 %) , 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 = 6.5Hz ,2H , Ar-CH_2) ,4.10(t, J = 6.5Hz ,*N*-CH_2),6.15(s, 1H CH), 7.12(t,J = 7.5Hz ,1H,quinolizine H-9), 7.43 (d,J = 7.5Hz , ,1H,quinolizine H-8),7.7(d,J = 7.5Hz ,1H, quinolizine H-10),9.17(s, 1H, OH), 16.65(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** : Colorless needles (3.2g, 60 %) , from ethanol / DMF ,m.p. 245-247^{o}C ; IR (ν /cm^{-1}): 3422 (OH), 1607 (CO), ^{1}H-NMR (DMSO-d_6) (δ,ppm): 2.39 (m , 2H ,CH_2),2.88(t, J = 6.5Hz ,2H , Ar-CH_2) ,4.10(t, J = 6.5Hz ,*N*-CH_2),6.25(s, 1H CH), 7.22(t,J = 7.5Hz ,1H,quinolizine H-9), 7.45 (d,J = 7.5Hz , ,1H,quinolizine H-8),7.72(d,J = 7.5Hz ,1H, quinolizine H-10). *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** : Colorless needles (3.3g, 60 %) , from ethanol / DMF ,m.p.230-232^{o}C ; IR (ν /cm^{-1}): 3449 (OH), 1624(CO), ^{1}H-NMR (DMSO-d_6) (δ,ppm): 2.49 (m , 2H ,CH_2),2.94(t, J = 6.5Hz ,2H , Ar-CH_2) ,4.12(t, J = 6.5Hz ,*N*-CH_2) ,6.17(s, 1H CH), 7.12(t,J = 7.5Hz ,1H,quinolizine H-9), 7.42 (d,J = 7.5Hz , 1H,quinolizine H-8),7.75(d,J = 7.5Hz ,1H, quinolizine H-10). *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.

3.Results and Discussion

It has been found that ,the reaction of 3-acetyl-4-hydroxyquinolin-2(1*H*)-ones **1a,b** with arylmethylenenitriles **2a-c,g** in ethanol and in the presence of catalytic amounts of piperidine ,resulted in the formation ,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**. 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 [12-15]. Compounds **1** may be existing as 4-quinolone[12-15] , at which quinolin-3-position becomes more acidic than its acetyl group.Moreover,the steric effect in the intermediates **4** facilitate deacetylation process .The structures of compounds **6** were also confirmed by synthesizing them from reaction of 4-hydroxyquinolin-2(1*H*)-ones **1d,e** under the same reaction conditions(*cf.*Scheme 1).

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).

In contrast to the behavior of 3-acetyl-4-hydroxyquinolin-2(1*H*)-ones **1a,b** towards arylmethylenemalononitriles **2a-c** ,3-acetyl-1-benzyl-4-hydroxyquinolin-2(1*H*)-one **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-hydroxyquinolin-2(1*H*)-one **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).

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*)-one**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).

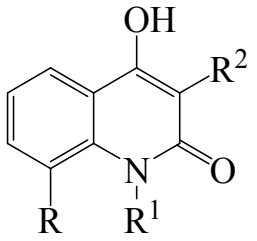
Also, refluxing of 2-acetyl-1-hydroxy-6,7-dihydropyrido[3,2,1-*ij*] quinolin-3(5*H*)-one **1c** ethoxymethylenemalononitrile **16** in absolute ethanol containing catalytic amounts of piperidine resulted in the formation of 11-imino-4*H*,5*H*,6*H*,9*H*-benzo [*ij*][2,3-*b*]quinolizin-8-one **18** .Elemental 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**[16] 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-dimethylamino propionate **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 intermwdiate **20** and then cyclised through methanol elimination to yield **21**(*cf.*Scheme 6).

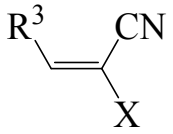
On the other hand ,cyclocondensation of 1-hydroxy-6,7-dihydropyrido [3,2,1-*ij*] quinolin-3(5*H*)-one **1g** [16] with methyl 2-benzolyamino-3-dimethylamino propionate **19** in refluxing acetic acid resulted in the formation of *N*-(8,11-dioxo-5,6,8,11-tetrahydro-4*H*-pyrano[3,2-*c*]pyrido[3,2,1-*ij*]quinolin-10-yl)benzamide **22** *via* dimethylamine and methanol elimination (*cf.*Scheme 6).

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,^{1}H-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).



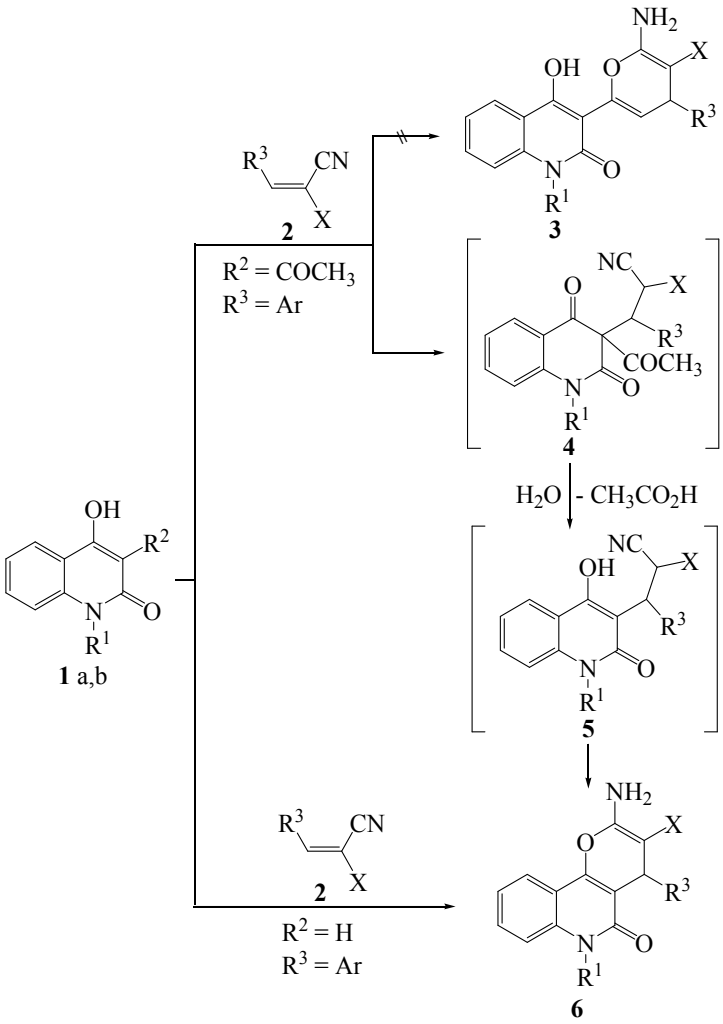
1

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



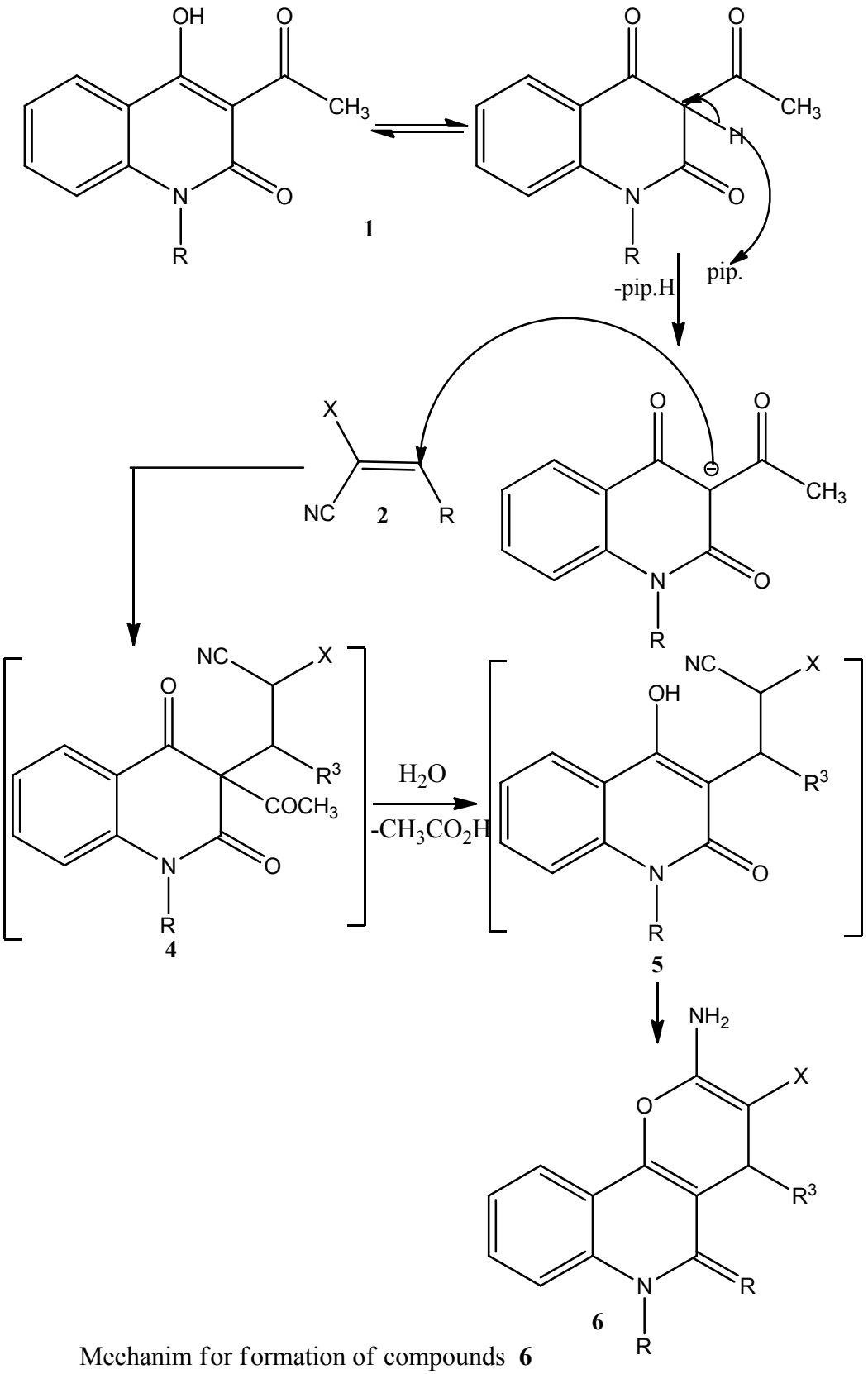
2

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	$C_6H_4OPh(m)$	$CO_2C_2H_5$

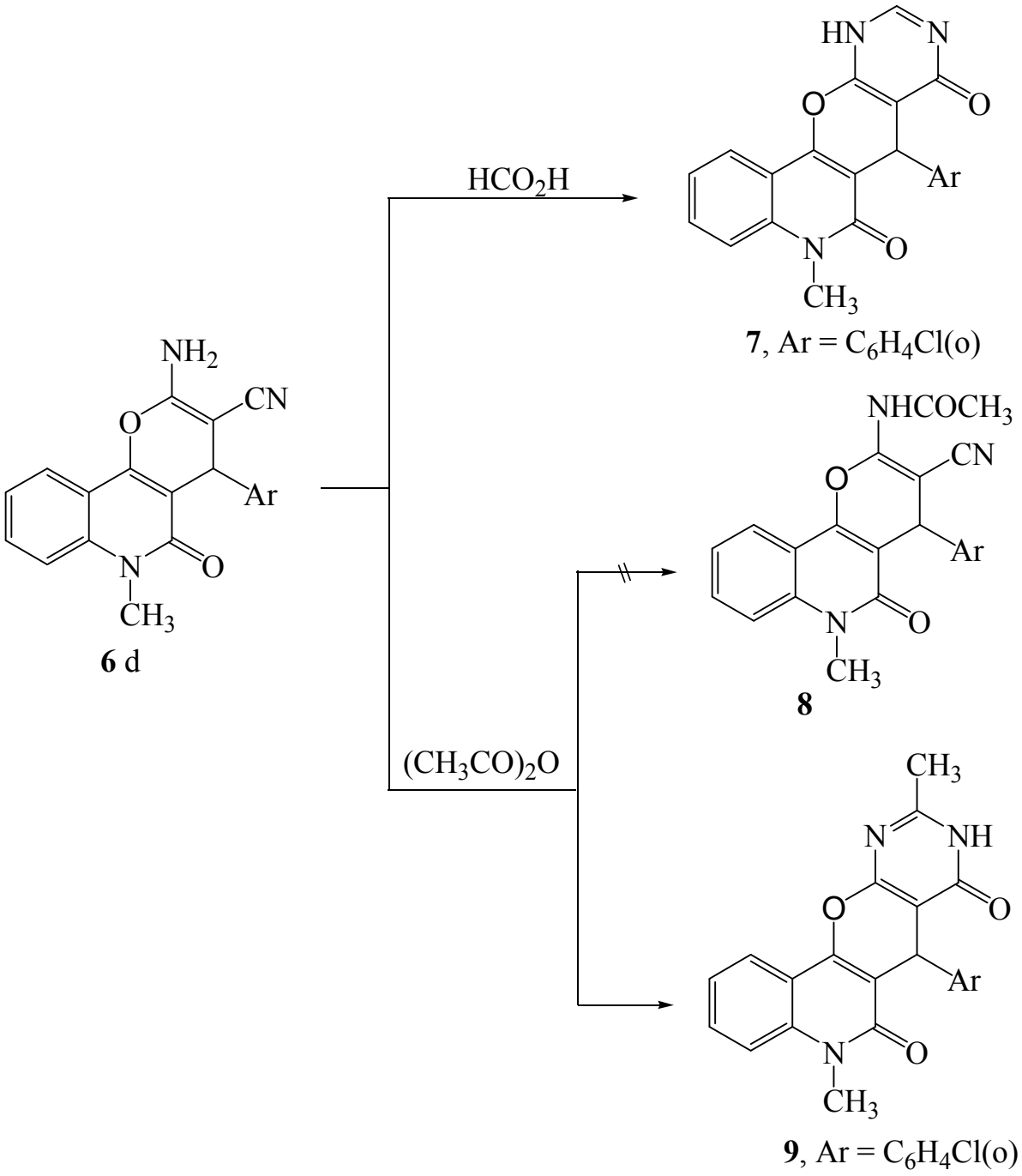


6	R^1	R^3	X
a	C_2H_5	C_6H_4OPh(m)	CN
b	C_2H_5	C_6H_4Cl(o)	CN
c	C_2H_5	$C_6H_4NO_2$(o)	CN
d	CH_3	C_6H_4Cl(o)	CN
e	CH_3	C_6H_4OPh(m)	CN
f	C_2H_5	C_6H_4OPh(m)	$CO_2C_2H_5$

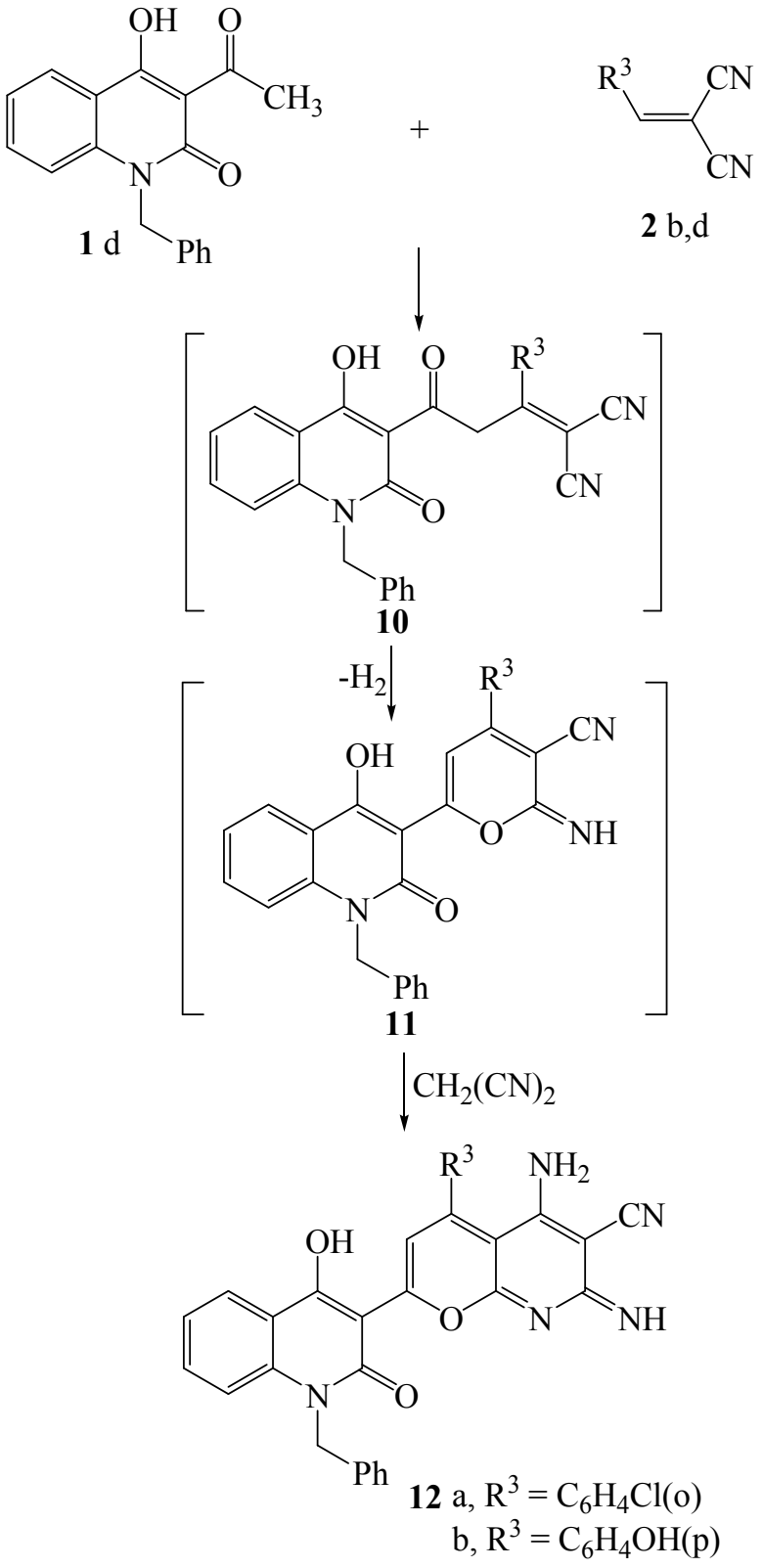
Scheme **1**: Synthesis of 4*H*-pyrano[3,2-*c*]quinolines **6a-e**.



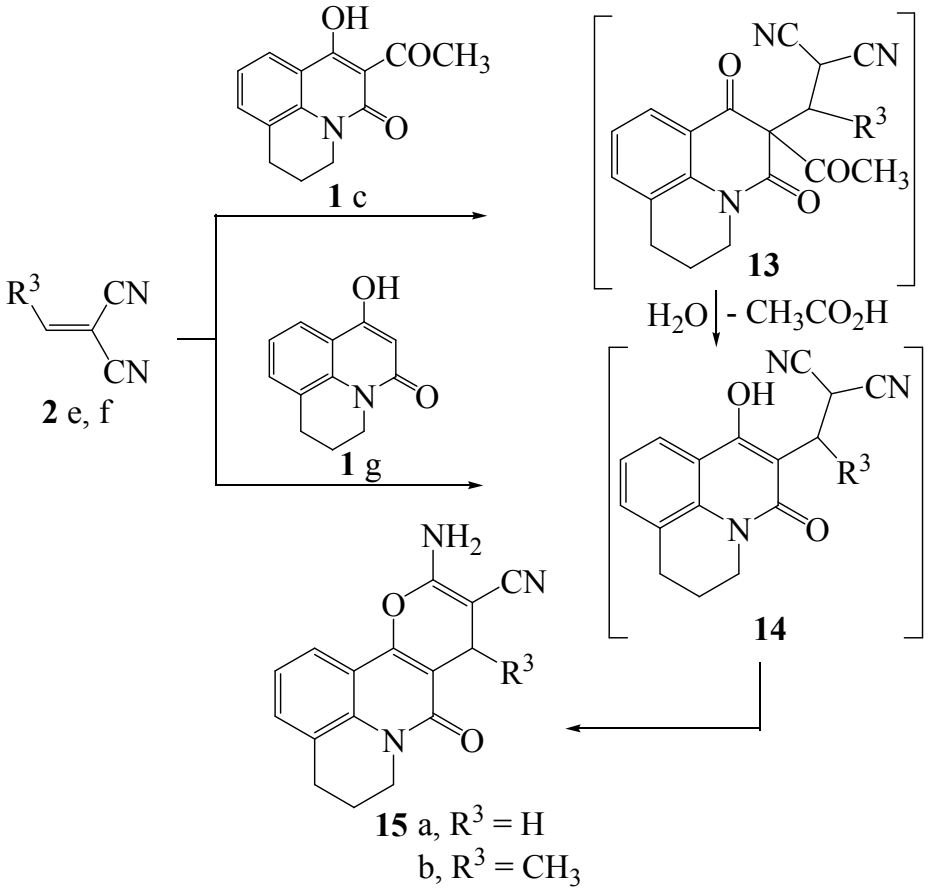
Mechanim for formation of compounds **6**



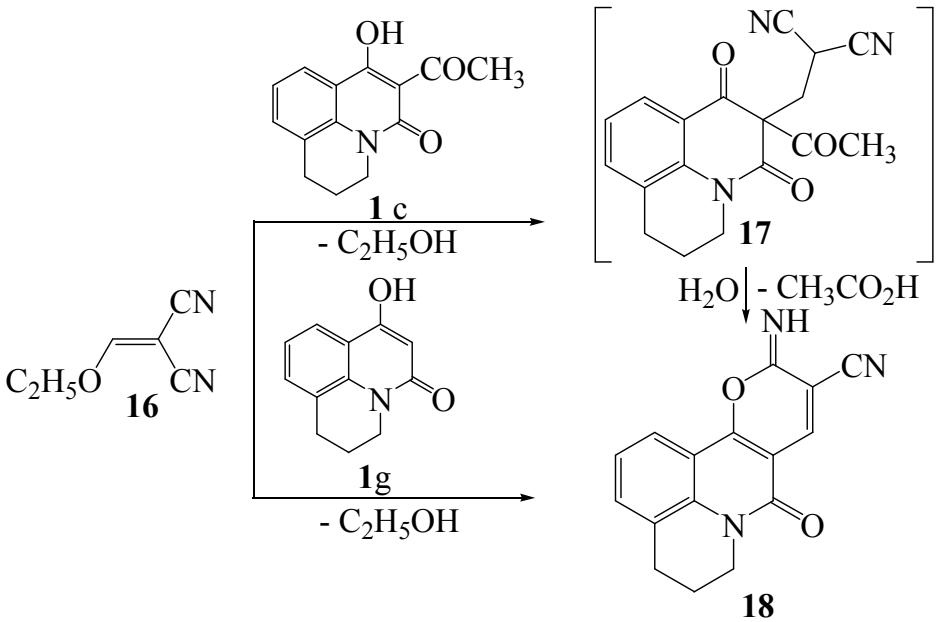
Scheme **2**: Reaction of **6d** with formic acid and acetic anhydride.



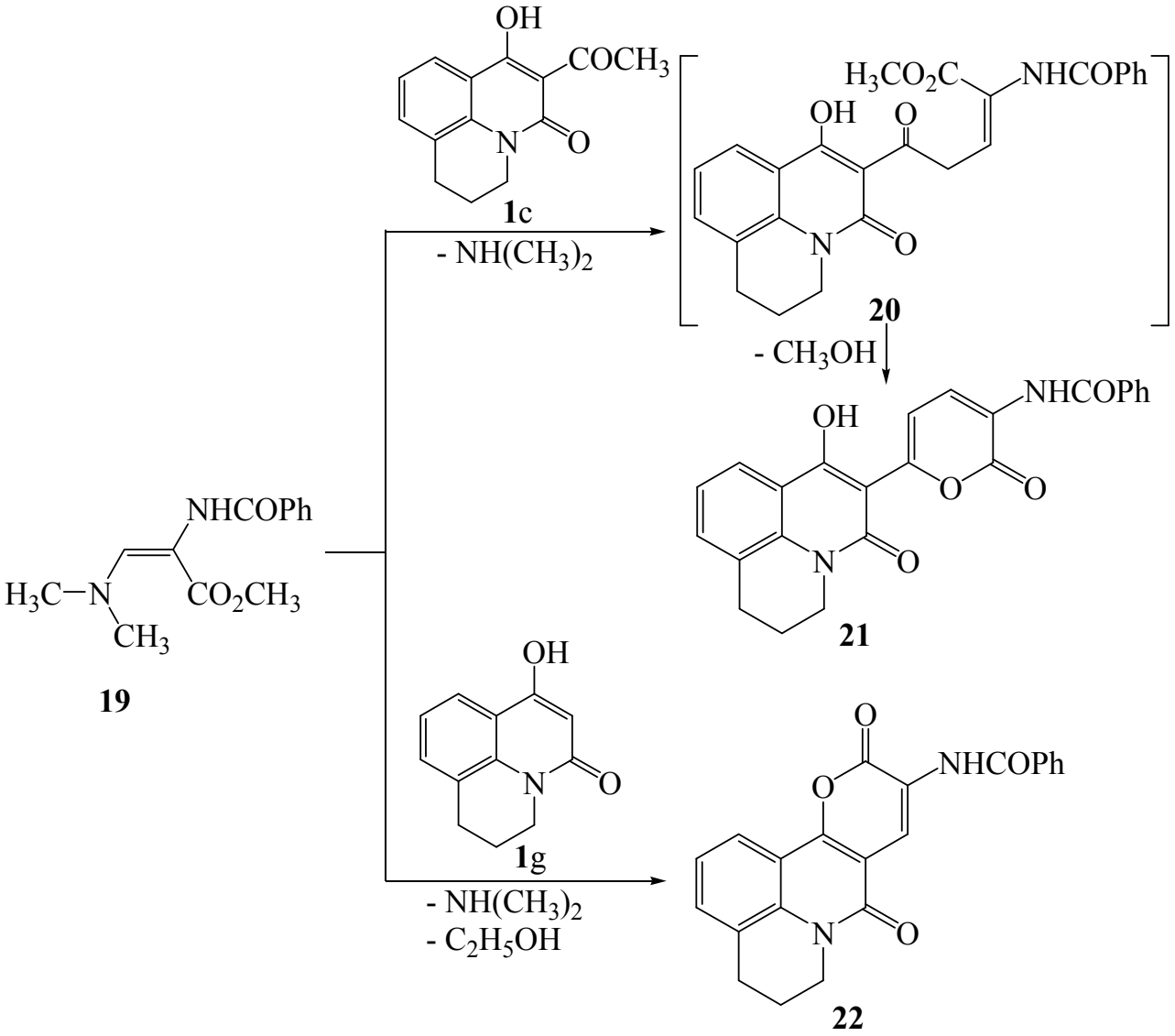
Scheme **3**:Formation of pyrano[2,3-b]pyridines **12a,b**.



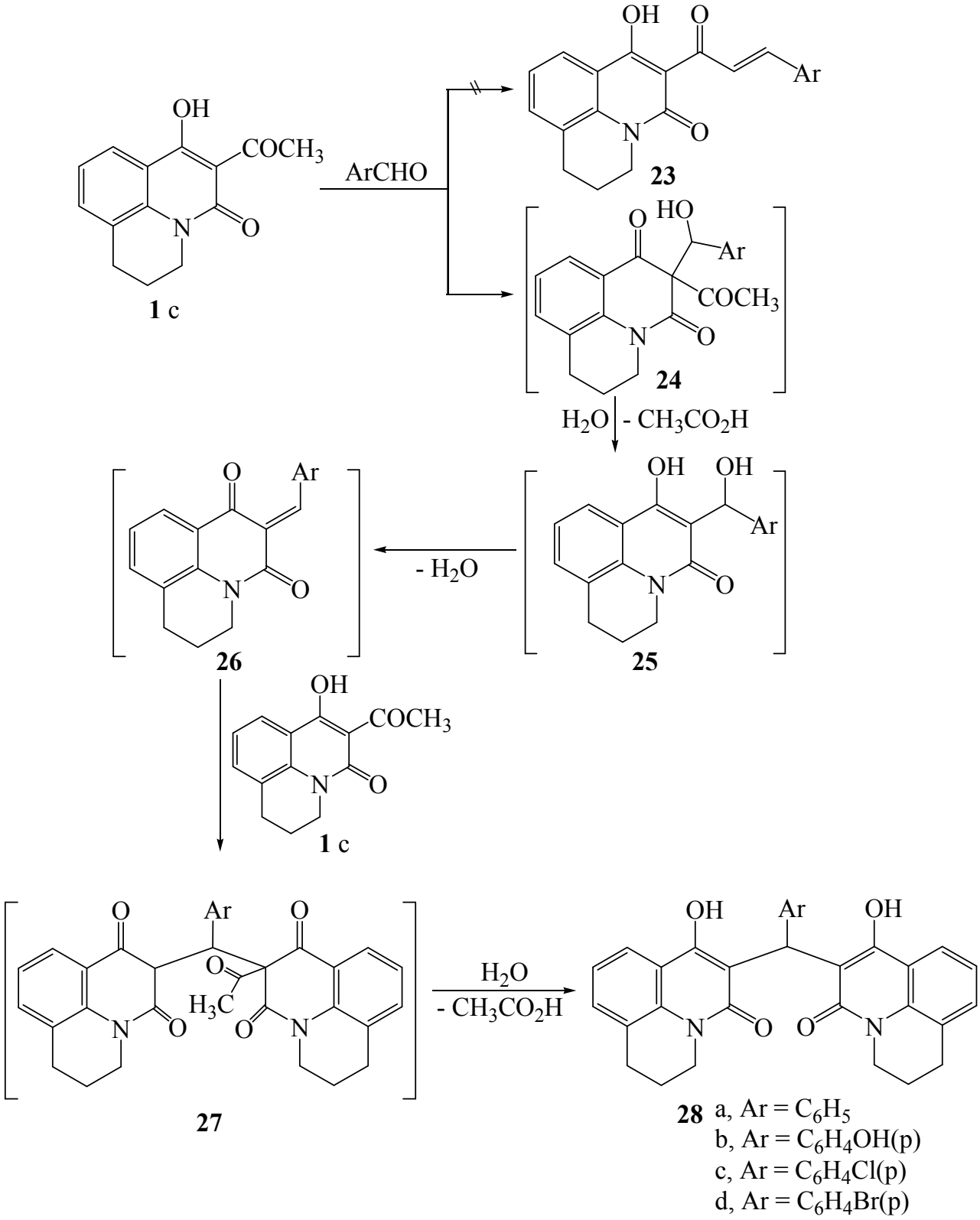
Scheme **4**: Synthesis of pyranoquinolines **15a,b**.



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



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



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

4.REFERENCES

[1] M.J.Mphahlele,"Synthesis of 2-Arylquinolin-4(1*H*)-ones and Their Transformation to *N*-alkylated and *O*-alkylated Derivatives," J.Heterocycl.Chem.,Vol.47 ,pp.1-14 (2010).doi:10.1002/jhet.279

[2] A.Abass ,E.A.Mohamed , M.M.Ismail and A.S.Mayas,"Substituted Quinolone.Part 16.preparation and Reactions of 3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid," Eur.J.Chem.,Vol.2, No.3,pp. 378-387 (2011).doi:10.5155/eurjchem.2.3.378.351

[3] N.G.Kozlov,K.N.Gusak and A.P.Kadutskii,"Development of the Catalytic Synthesis of Compounds of the Quinoline Series,"Chem.of Heterocycl. Compounds ,"Vol.46, No.5,pp.505-528(2010).

[4] H.M.Hassanin and D.Abdel-Kader ,"Synthesis of Some Novel binuclear Heterocyclic Compounds From 6-Ethyl-3-nitropyrano[3,2-*c*]quinolin-4,5(6*H*)-dione,Heterocycles,"Vol.87,No.2,pp -369-380 (2013).doi:10.3987/COM-12-12639

[5] A.M,El-Agrody and A.M.Al-Ghamdi ,"Synthesis of certain Novel 4*H*-pyrano[3,2-*h*]quinoline Derivatives," Arkivoc , Vol. (xi),pp-134-136 (2011) .

[6] M.A.Ibrahim,H.M.Hassanin ,Y.A.Gabr and Y.A.Alnamer ,"Studies on the Chemical Behavior of 3-(Nitroacetyl)-1-ethyl-4-hydroxyquinolin-2(1*H*)-one Towards Some Electrophilic and Nucleophilic Reagents, "J.Braz .Chem. Soc., Vol.23,No.5,pp.905-912(2012).

[7] G.B. Okide,"A short Synthesis of 5,7-bis(dialkylamino)-2-methyl-8-hydroxyquinolines ," J.Heterocycl. Chem ., Vol.38,No.5, pp.1213- 1214 (2001) .doi :10. 1002 / jhet .5570380529.

[8] F.E.L.Mariah,"Synthesis and antimicrobial activities of pyrano[3,2-*c*]quinoline, pyrimido [5',4':5,6]pyrano[3,2-*c*]quinoline and [1,2,4]triazolo[2",3";:1',6']pyrimido [5',4':5,6]pyrano[3,2-*c*]quinoline derivatives," J.Chem.Res.,Vol. 9,No. 5,588-592(2009).

[9] H.M.Hassanin,"Nucleophilic Substitution and Ring Transformation Reactions with 4-Chloro-6-ethyl-3-nitropyrano[3,2-c]quinoline-2,5-(6*H*)-diones, " Arkivoc, (vi),pp.384-397(2012).

[10] F.M.A.El-Taweel,M.A.Sofan M.A.Mashaly , M.A.Hanna and A.A.El-Agamey,"Synthesis of Some New Pyranoquinoline , pyridine and Pyrone Derivatives," Die Pharmazie ,Vol.45,No. 9,671-673(1990).

[11] M.Rufchahi and A.G.Gilani,"Synthesis ,Characterization and Spectroscopic Properties of Some New Disperse Dyes Derived From 4-hydroxybenzo[*h*]quinolin-2-(1*H*)-one as a new Synthesized Enol Type Coupling Component ,"Dyes and Pigments ,Vol.95,No. 3,pp.632-636(2012).
[12] F.M.A.El-Taweel , S.Z.A.Sowellim and A.A.El-Agamey ,"Reactions with 2(1*H*)-quinolone and Coumarin Derivatives: New Routes To Polysubstituted 2 (1*H*)-quinolone and Coumarin Derivatives ,"Bull .Chem . Soc . Jpn.,68,pp.905 – 910 (1995).
[13] F.M.A.El-Taweel ,D.A.Ibrahim and M.A.Hanna ,"Synthesis of Some New Quinoline Derivatives : New Routes To Synthesize Polysubstituted 2(1*H*)-quinolone Derivatives, " Boll .Chim .Farm .,Vol. 140, No.5 ,pp. 287-296 (2001).
[14] A.A.El-Agamey ,A.A.Aboattaia and F.M.A.El-Taweel,"Studies on 2(1*H*)-quinolone Derivatives : Synthesis of Some New 4*H*-pyrano[3,2-**c**] quinoline ,6*H*-isochromeno[4,3-*c*]quinoline and 2-Oxoquinolin-3-ylthieno[2,3-*b*]pyridine carboxamide Derivatives," Alex.J.Pharm.Sci.,Vol. 26,No.1,pp. 32-38(2012).
[15] F.M.A.El-Taweel and A.A.El-Agamey," New and Facile Synthesis of Substituted Pyrrole , Pyridine , Pyrazolo[4,3-*b*] pyridine, Pyrano[3,2-*c*] quinoline , Napthopyran, Naphthodipyran and Coumarin Derivatives," Intern.J.Org . Chem., Vol.3,pp.58-70(2013).
[16]P.Roschger ,W.Fiala and W.Stadlbauer ,"Nucleophilic Substitution and Ring Closure Reactions of 4-Chloro-3-nitro-2-quinolones," J.Heterocycl .Chem., Vol. 29, pp.225-231(1992).