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**THE REACTIVITY OF 8-HYDROXYQUINOLINE AND ITS
DERIVATIVES TOWARD α -CYANOCINNAMONITRILES AND ETHYL
 α -CYANOCINNAMATES: SYNTHESIS, REACTIONS, AND
APPLICATIONS OF 4*H*-PYRANO[3,2-*h*]QUINOLINE DERIVATIVES**

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Abstract – The main purpose of this review is to present a literature survey on the reactivity of 8-hydroxyquinoline and its derivatives toward α -cyanocinnamitrile or ethyl α -cyanocinnamate derivatives, which leads to the formation of a variety of 4*H*-pyrano[3,2-*h*]quinoline derivatives. The reactions of the synthesized β -enaminonitriles and β -enaminoesters with different electrophilic followed by nucleophilic reagents were also explored. Some of these reactions provided successful routes to produce biologically important privileged structures.

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1. INTRODUCTION

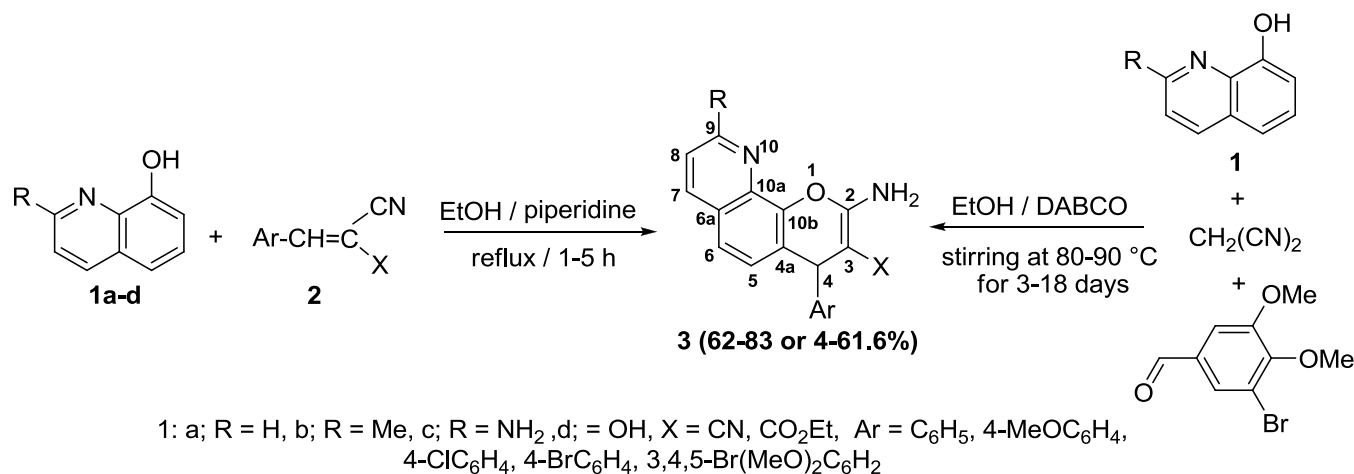
A variety of 4*H*-pyrans and condensed 4*H*-pyrans were prepared recently by utilizing nitriles as starting materials.¹⁻⁷ The α -cyanocinnamionitrile or ethyl α -cyanocinnamate derivatives reacted with different aromatic and heterocyclic compounds containing hydroxyl group to produce condensed 4*H*-pyrans derivatives.⁸⁻¹⁴ Due to the wide spectrum of activities shown by 4*H*-pyran moiety, various substituted 4*H*-pyrano[3,2-*h*]quinoline and their condensed analogues have been synthesized. In sequel, the main purpose of this review is to present a survey on the chemistry of 8-hydroxyquinoline and its derivatives toward α -cyanocinnamionitrile or ethyl α -cyanocinnamate derivatives in the last fifteen years, as well as to explore the reactions of the synthesized β -enaminonitriles and β -enaminoesters with different electrophilic followed by nucleophilic reagents. The chemistry of quinoline and fused quinoline derivatives has attracted many researchers due to their biological activities and their potential applications as pharmacological agents. Many compounds that synthesized from 8-hydroxyquinoline and its derivatives possess diverse therapeutic activities such as antifungal,¹⁵ antibacterial,¹⁶⁻¹⁸ antiprotozoic drugs as well as antineoplastics¹⁹ and antiproliferative^{20,21} activities. In addition styrylquinoline derivatives have been explored as potential HIV integrase inhibitors²²⁻²⁸ and also for their extensive biological activities.²⁹⁻³³ Furthermore, 4*H*-pyrano[3,2-*h*]quinoline and fused 4*H*-pyrano[3,2-*h*]quinoline derivatives display *in-vitro* antimicrobial^{12,34-36} and/or antitumor³⁷⁻³⁹ activities. A more extensive study for these compounds is crucial to determine additional antitumor parameters to give a deeper insight to their structure activity relationship. This series of molecules can be used in large scale in development of antitumor therapeutics.

2. SYNTHESIS OF 2-AMINO-4*H*-PYRANO[3,2-*h*]QUINOLINE DERIVATIVES

2-1. From 8-hydroxyquinoline and 2-substituted 8-hydroxyquinoline

Treatment of 8-hydroxyquinoline and 8-hydroxy-2-methylquinoline (**1a,b**) with α -cyanocinnamionitriles (**2**) (Ar = 4-Cl/BrC₆H₅) in ethanolic piperidine under reflux for 1-5 h gave 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile⁸ (R = H, Me) (**3**), while reaction of 8-hydroxyquinoline (**1a**) with α -cyanocinnamionitriles and ethyl α -cyanocinnamates (**2**) (Ar = C₆H₅, 4-MeOC₆H₅) afforded 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile and ethyl 2-amino-4-aryl-4*H*-pyrano-[3,2-*h*]quinoline-3-carboxylate derivatives⁴⁰ (R = H) (**3**) in 62-83% yield, respectively (Scheme 1). Attempts to react 8-hydroxyquinoline and 8-hydroxy-2-methylquinoline (**1a,b**) with ethyl α -cyano-*p*-chloro/bromocinnamates (**2**) was unsuccessful, the ester derivatives **3** were not formed.⁸ Furthermore, the three components reaction of 8-hydroxyquinoline, 8-hydroxy-2-methylquinoline, 2-amino-8-hydroxyquinoline and 2,8-quinolinediol (**1a-d**), malononitrile and 3-bromo-4,5-dimethoxy-benzaldehyde in ethanol at room temperature, charged with 1,4-diazabicyclo[2.2.2]octane (DABCO) and then stirred at 80 °C under LC-MS control for 3-18 days afforded 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-pyrano[3,2-

h]quinoline-3-carbonitrile³⁹ (**3**) (R = H, Me, NH₂, OH) in 4-61.6% yield, respectively (Scheme 1).



Scheme 1. Synthesis of 4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile and ethyl 4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives (**3**)

The formation of **3** indicates that the phenolate anion (C-7) of **1** attacks at the electrophilic β -carbon of **2** to yield an acyclic Michael adduct, which underwent cyclization to afforded **3** as shown in Figure 1.

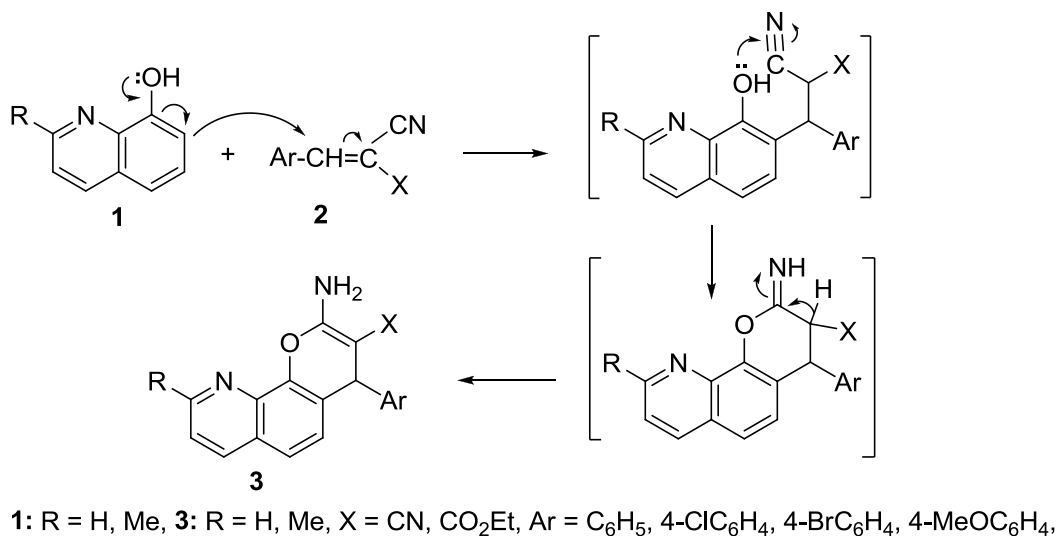
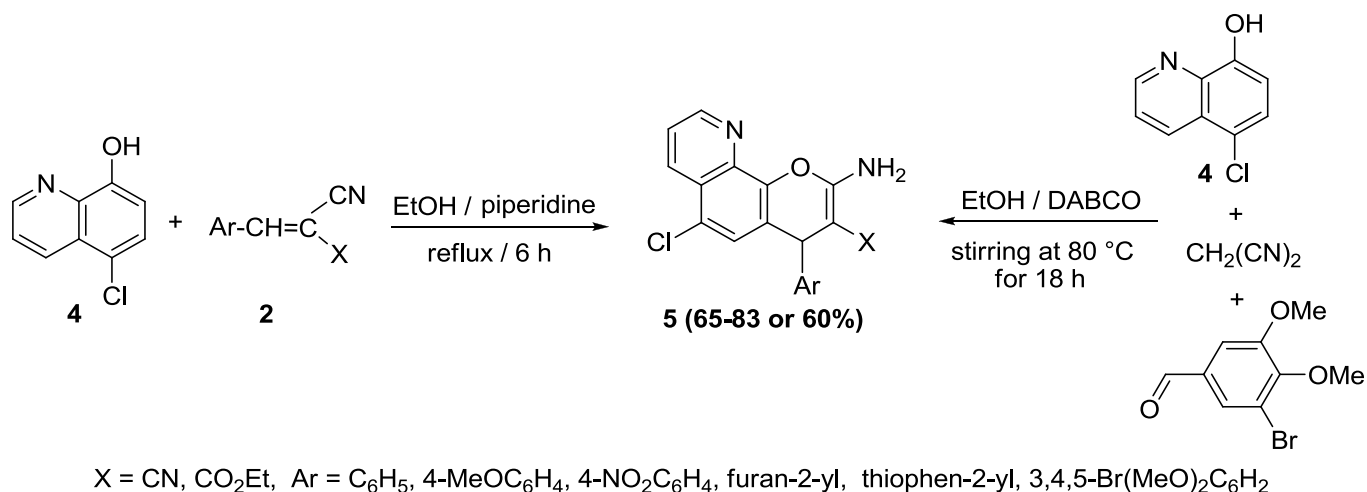


Figure 1. Mechanism of the formation of compound **3**

2-2. From 5-chloro-8-hydroxyquinoline

The reaction of 5-chloro-8-hydroxyquinoline (**4**) with α -cyanocinnamoyl nitriles and ethyl α -cyano-cinnamates (**2**) in ethanolic piperidine under reflux for 6 h afforded 2-amino-4-aryl-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile^{12,36} and ethyl 2-amino-4-aryl-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives³⁵ (**5**) in 65-83% yield, respectively (Scheme 2). Furthermore, the three components reaction of 5-chloro-8-hydroxyquinoline (**4**), malononitrile and 3-bromo-4,5-dimethoxy-

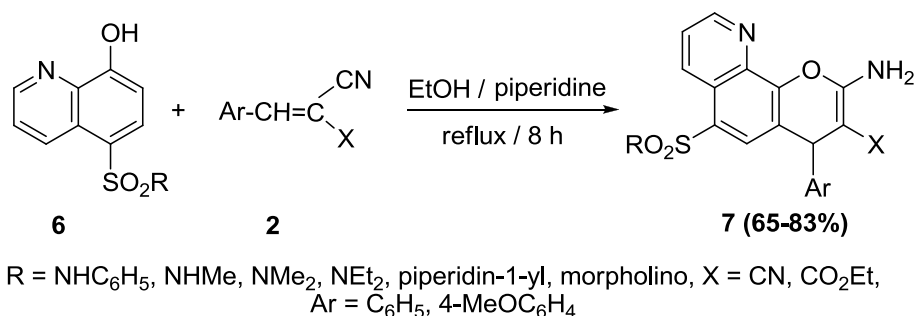
benzaldehyde in ethanol at room temperature, charged with 1,4-diazabicyclo[2.2.2]octane (DABCO) and then stirred at 80 °C under LC-MS control for 18 h afforded 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile³⁹ (**5**) in 60% yield (Scheme 2).



Scheme 2. Synthesis of 6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile and ethyl 6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives (**5**)

2-3. From 8-hydroxyquinoline-5-sulfonamide

Treatment of 8-hydroxyquinoline-5-sulfonamide (**6**) with α -cyanocinnamionitriles and ethyl α -cyanoacrylates (**2**) in ethanolic piperidine under reflux for 8 h afforded 2-amino-4-aryl-3-cyano-4*H*-pyrano[3,2-*h*]quinoline-6-sulfonamide¹⁴ and ethyl 2-amino-4-aryl-6-sulfamoyl-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives¹⁴ (**7**) in 65-83% yield, respectively (Scheme 3).

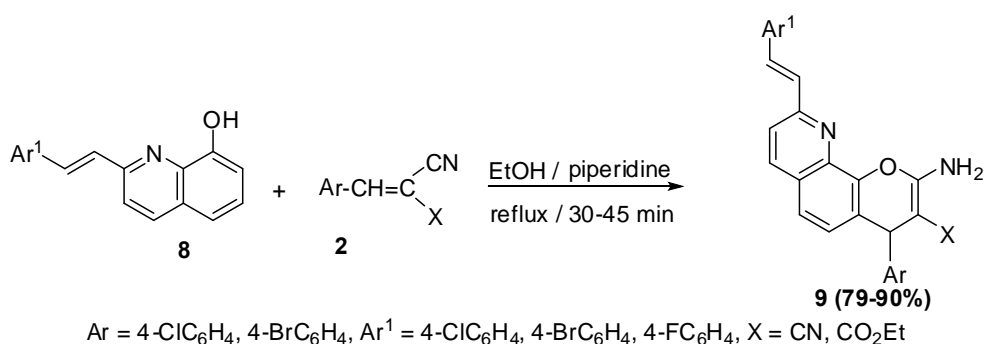


Scheme 3. Synthesis of 4*H*-pyrano[3,2-*h*]quinoline-6-sulfonamide and ethyl 6-sulfamoyl-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives (**7**)

2.4. From (*E*)-2-(4-halostyryl)-8-hydroxyquinoline

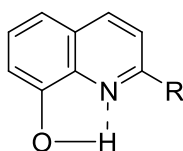
Treatment of (*E*)-2-(4-halostyryl)-8-hydroxyquinoline (**8**) with α -cyanocinnamionitriles and ethyl α -

cyanocinnamates (**2**) in ethanolic piperidine under reflux for 30-45 min gave (*E*)-2-amino-4-aryl-9-(4-halostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile^{8,37} in 81-90% yield and ethyl (*E*)-2-amino-4-aryl-9-(4-halostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives^{8,37} (**9**) in 79-82% yield, respectively (Scheme 4). The relative *E* configuration of compounds **9** were established from the coupling constant values^{8,37} ($J = 16-16.5$ Hz).



Scheme 4. Synthesis of (*E*)-9-(4-halostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile and ethyl (*E*)-9-(4-halostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives (**9**)

The tendency of the 8-hydroxyquinoline, 8-hydroxy-2-methylquinoline (**1a,b**) and (*E*)-2-(4-halostyryl)-8-hydroxyquinoline (**8**) towards the electrophilic β -carbon of α -cyano-*p*-chloro/bromocinnamionitriles and ethyl α -cyano-*p*-chloro/bromocinnamates (**2**) follows the sequence 8-hydroxy-2-styrylquinoline (**8**) > 8-hydroxyquinoline (**1a**) > 8-hydroxy-2-methylquinoline (**1b**) as shown in Figure 2.



1: a; R = H, b; R = Me, **8**: R = 4-F-styryl, 4-Cl-styryl, 4-Br-styryl

Figure 2

Thus, the reactivity was enhanced with the presence of the styryl group (conjugation effect) in the 2-position, while the presence of methyl group in the 2-position suppress the reactivity via (+I effect), in addition to the expected hydrogen bond formation as shown in Figure 3.

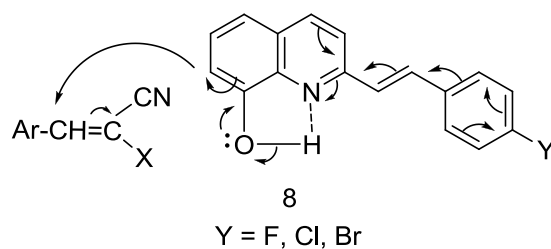
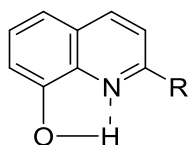


Figure 3

Also, this observation was supported by the easy attacks of phenolate anion (C-7) of **8** at the electrophilic β -carbon of ethyl α -cyano-*p*-chloro/bromocinnamates (**2**) rather than **1a,b** to yield an acyclic Michael adduct, which underwent cyclization to give the ester **9** (X = CO₂Et) as illustrate in Figure 1.

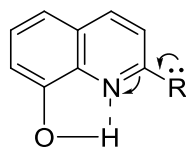
In case of 2-amino-8-hydroxyquinoline and 2,8-quinolinediol (**1c,d**) the tendency of **1c,d** towards the electrophilic β -carbon of α -cyanocinnamionitriles (**2**) follows the sequence 2-amino-8-hydroxyquinoline (**1c**) > 2,8-quinolinediol (**1d**) as shown in Figure 4.



1: c; R = NH₂, d; R = OH

Figure 4

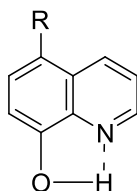
Thus, the reactivity was enhanced with the presence of the amino group in the 2-position rather than the hydroxyl group and this was explained through the resonance effect which activated the quinoline ring towards the electrophilic β -carbon of α -cyanocinnamionitrile derivatives (**2**) and also, the amino group accommodate the positive charge rather than hydroxyl group as shown in Figure 5.



R = NH₂, OH

Figure 5

In addition, the tendency of the 5-chloro-8-hydroxyquinoline (**4**) and 8-hydroxyquinoline-5-sulfonamide (**6**) towards the electrophilic β -carbon of α -cyanocinnamionitrile and ethyl α -cyanocinnamate derivatives (**2**) follows the sequence 5-chloro-8-hydroxyquinoline (**4**) > 8-hydroxyquinoline-5-sulfonamide (**6**) as shown in Figure 6.



4: R = Cl, **6**: R = NHSO₂R

Figure 6

Thus, the reactivity was enhanced with the presence of the chloro atom in the 5-position rather than the

sulfonamide group because the chloro atom act as weakly deactivating the quinoline ring through (-I effect) as shown in Figure 7, while the sulfonamide group act as strongly deactivating the quinoline ring through (-I effect) as shown in Figure 8.

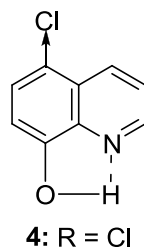


Figure 7. The effect of the inductive effect of chloro group at 5-position

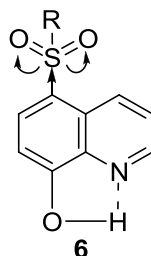


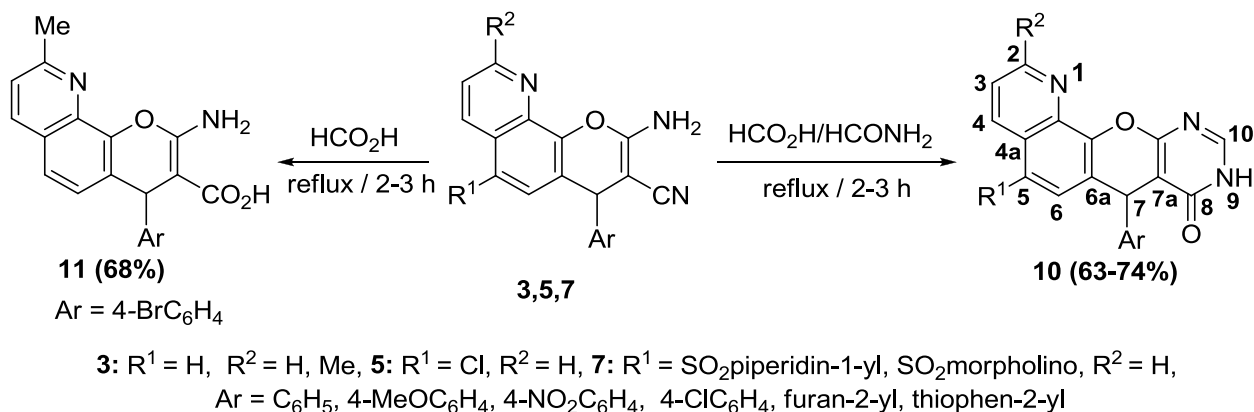
Figure 8. The effect of the inductive effect of sulfonamide group at 5-position

3. REACTIONS OF 2-AMINO-4*H*-PYRANO[3,2-*h*]QUINOLINE DERIVATIVES WITH ELECTROPHILIC REAGENTS

3-1. Reactions with carboxylic acid derivatives

3-1-1. Reactions with formic acid

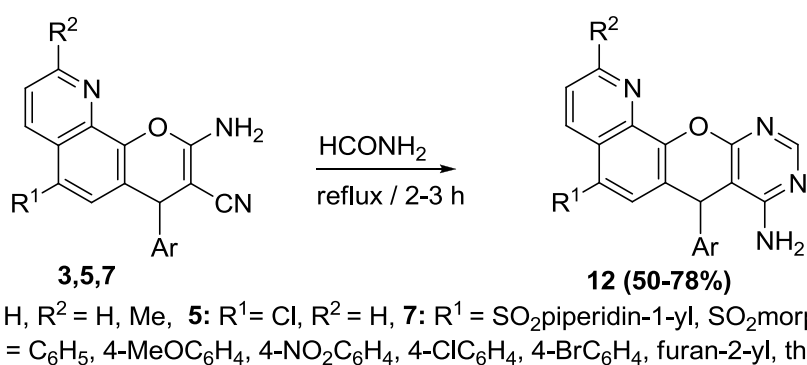
Condensation of the β -enaminonitriles **3**, **5** and **7** with formic acid or formic acid/formamide under reflux for 2-3 h proceeded via the addition of the formic acid on the amino group of β -enaminonitriles followed by cyclization and Dimroth rearrangement via nucleophilic attack of the oxygen atom of the hydroxyl group on the cyano group to gave 7-aryl-7*H*,9*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8-one derivatives^{12,14,34,40} (**10**) in 63-74% yield (Scheme 5). In a similar manner, reaction of the β -enaminonitrile **3** (Ar = 4-BrC₆H₄) with formic acid under reflux for 2 h afforded the 2-amino-4-(4-bromophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylic acid³⁴ (**11**) in 68% yield via acid hydrolysis of the cyano group of **3** to carboxylic group (Scheme 5).



Scheme 5. Synthesis of 7*H*,9*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8-ones (**10**) and 4*H*-pyrano[3,2-*h*]quinoline-3-carboxylic acid (**11**)

3-1-2. Reactions with formamide

The reaction of the β -enaminonitriles **3**, **5** and **7** with formamide under reflux for 2-3 h proceeded via condensation of the amino group of β -enaminonitriles with formamide followed by cyclization via nucleophilic attack of the nitrogen atom of the amino group on the cyano group to provided 8-amino-7-aryl-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives^{12,14,40,41} (**12**) in 50-78% yield (Scheme 6).

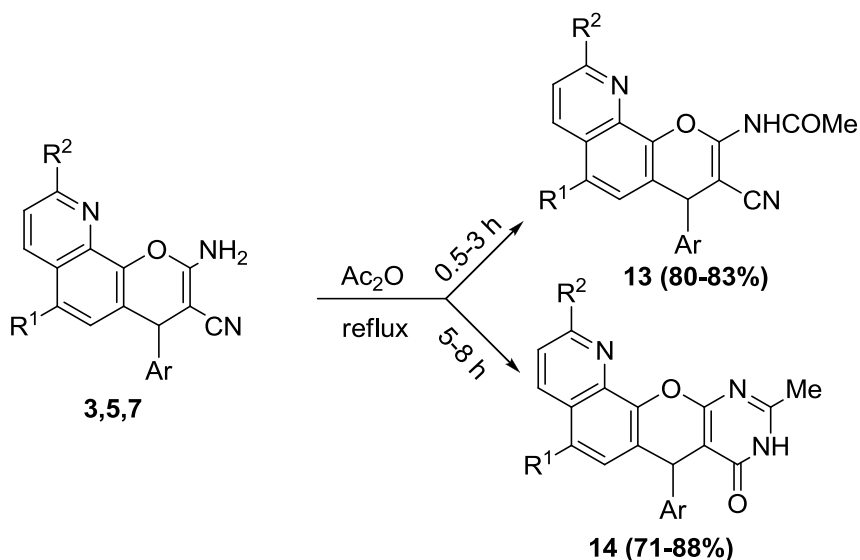


Scheme 6. Synthesis of 7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**12**)

3-1-3. Reactions with acetic anhydride

Treatment of the β -enaminonitriles **3**, **5** and **7** with acetic anhydride under reflux for 0.5 or 3 h give 2-acetylamino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives^{12,14,40,41} (**13**) in 80-83% yield, via nucleophilic attack of the nitrogen atom of the amino group on the carbonyl group of acetic anhydride, while boiling of **3**, **5** and **7** with acetic anhydride or acetic anhydride/pyridine for 5-8 h afforded the corresponding 7-aryl-10-methyl-7*H*,9*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8-one derivatives^{12,14,40,41} (**14**) in 71-88% yield, respectively (Scheme 7) via acylation of the amino group followed by cyclization

and Dimroth rearrangement by nucleophilic attack of the oxygen atom of the hydroxyl group on the cyano group.

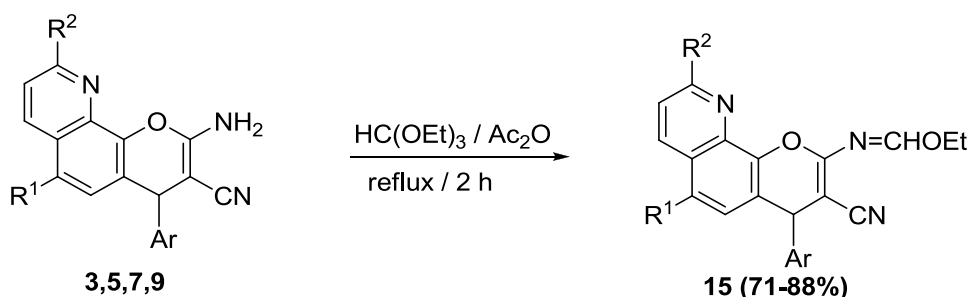


3: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, Me, **5**: $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{H}$, **7**: $\text{R}^1 = \text{SO}_2\text{piperidin-1-yl}$, $\text{SO}_2\text{morpholino}$, $\text{R}^2 = \text{H}$,
 $\text{Ar} = \text{C}_6\text{H}_5$, 4-MeOC₆H₄, 4-NO₂C₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, furan-2-yl, thiophen-2-yl

Scheme 7. Synthesis of 2-acetylamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**13**) and 10-methyl-7*H*,9*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8-one derivatives (**14**)

3-1-4. Reactions with triethyl orthoformate

Treatment of the β -enaminonitriles **3**, **5**, **7** and **9** with triethyl orthoformate in acetic anhydride under reflux for 2 h gave the corresponding 4-aryl-2-ethoxymethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives^{12,14,40-42} in 71-88% yield and (*E*)-4-(4-chlorophenyl)-9-(4-chlorostyryl)-2-ethoxymethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile³⁸ (**15**) ($\text{R}^2 = 4\text{-Cl-styryl}$) in 81% yield, respectively (Scheme 8) through loss of 2 EtOH molecules. The relative *E* configuration of compounds **15** was established from the coupling constant values³⁸ ($J = 16$ Hz).



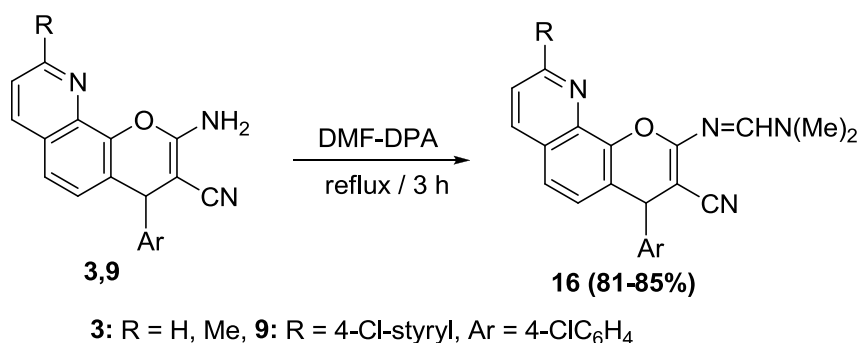
3: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, Me, **5**: $\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{H}$, **7**: $\text{R}^1 = \text{SO}_2\text{piperidin-1-yl}$, $\text{SO}_2\text{morpholino}$, $\text{R}^2 = \text{H}$, **9**: $\text{R}^1 = \text{H}$, $\text{R}^2 = 4\text{-Cl-styryl}$,

$\text{Ar} = \text{C}_6\text{H}_5$, 4-MeOC₆H₄, 4-NO₂C₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, furan-2-yl, thiophen-2-yl

Scheme 8. Preparation of 2-ethoxymethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**15**)

3-1-5. Reactions with dimethylformamide dipentyl acetal (DMF-DPA)

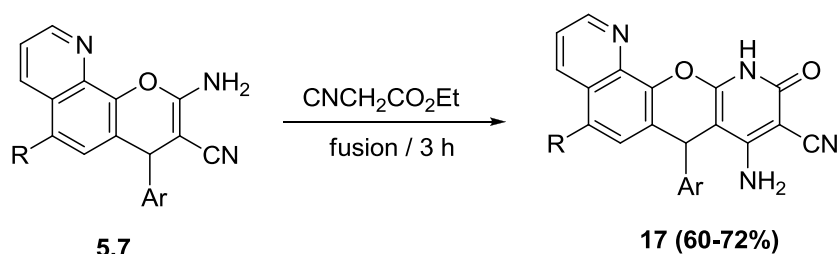
Condensation of the β -enaminonitriles **3** and **9** with DMF-DPA in benzene under reflux for 3 h gave the 4-(4-chlorophenyl)-2-dimethylaminomethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile⁴¹ in 83% yield, 4-(4-chlorophenyl)-2-dimethylaminomethyleneamino-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile⁴¹ in 81% yield and (*E*)-4-(4-chlorophenyl)-9-(4-chlorostyryl)-2-dimethylaminomethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile³⁸ (**16**) (R = 4-Cl-styryl) in 85% yield, respectively (Scheme 9). The relative *E* configuration of compounds **16** was established from the coupling constant values³⁸ ($J = 16.5$ Hz). The formation of **16** was explained according to the explanation described for compound **12**.



Scheme 9. Preparation of 2-dimethylaminomethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**16**)

3-1-6. Reactions with ethyl cyanoacetate

Treatment of the β -enaminonitriles **5** and **7** with ethyl cyanoacetate under fusion for 3 h gave 8-amino-7-aryl-5-chloro/sulfamoyl-9-cyano-10-oxo-pyrido[2',3':6,5]pyrano[3,2-*h*]quinoline derivatives^{12,42} (**17**) in 60-72% yield (Scheme 10). This can be explained through the nucleophilic addition of nitrogen atom of the amino group of β -enaminonitriles to the carbocation of the carbonyl group of ethyl cyanoacetate with elimination of EtOH followed by cyclization to give **17**.



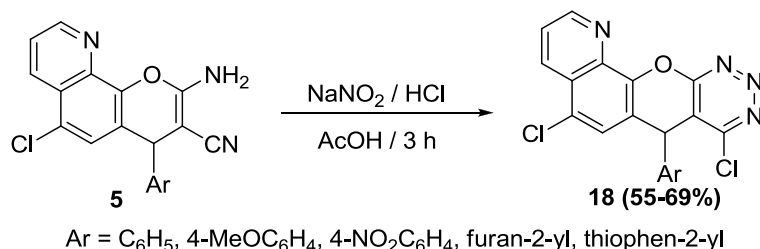
5: R = Cl, **7:** R = SO₂NMe₂, SO₂NEt₂, Ar = C₆H₅, 4-MeOC₆H₄, 4-NO₂C₆H₄, furan-2-yl, thiophen-2-yl

Scheme 10. Synthesis of 5-chloro/sulfamoyl-pyrido[2',3':6,5]pyrano[3,2-*h*]quinoline derivatives (**17**)

3-1-7. Reactions with sodium nitrite

Diazotization of the β -enaminonitriles **5** in acetic acid with an aqueous solution of sodium nitrite and

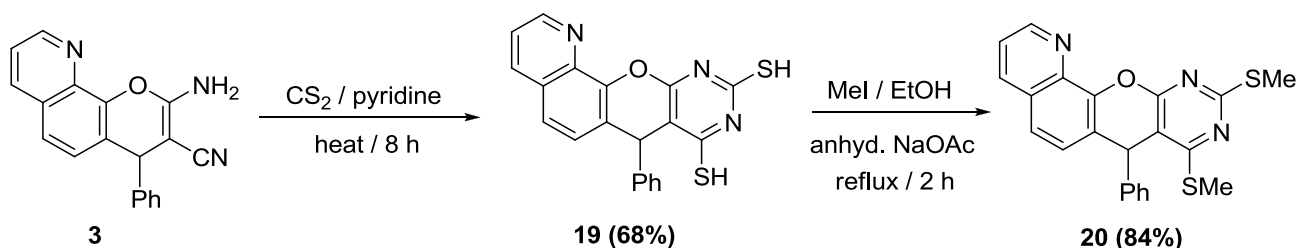
hydrochloric acid in ice cold solution under stirring for 3 h lead to the formation of the intermediate diazonium salt, which underwent cyclization to gave 5-aryl-4,7-dichloro-5*H*-[1,2,3]triazino[4',5':6,5]-pyrano[3,2-*h*]quinoline derivatives³⁶ (**18**) in 55-69% yield (Scheme 11).



Scheme 11. Synthesis of 4,7-dichloro-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**18**)

3-2. Reactions with carbon disulfide

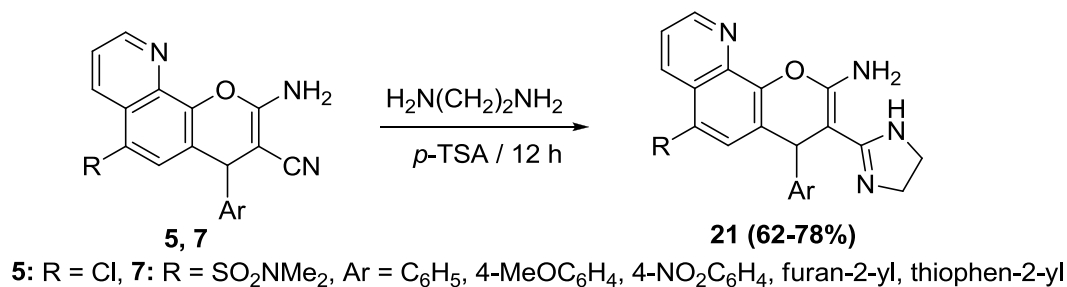
The mixture of 2-amino-4-phenyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**3**) with carbon disulfide in pyridine was heated in water bath for 8 h to give 7-phenyl-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline-8,10-dithiol⁴⁰ (**19**) in 68% yield. The reaction proceeded by the intermediate formation of 4-iminothiazine which rearranged rapidly and irreversibly by a base-catalyzed (pyridine) ring-opening, ring-closure sequence to give the observed product **19**. Methylation of **19** with methyl iodide in ethanol containing anhydrous sodium acetate under reflux for 2 h afforded the bis(methylthio) derivative⁴⁰ (**20**) in 84% yield (Scheme 12).



Scheme 12. Synthesis of 7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8,10-dithiol (**19**) and bis(methylthio) derivatives (**20**)

3-3. Reactions with ethylenediamine

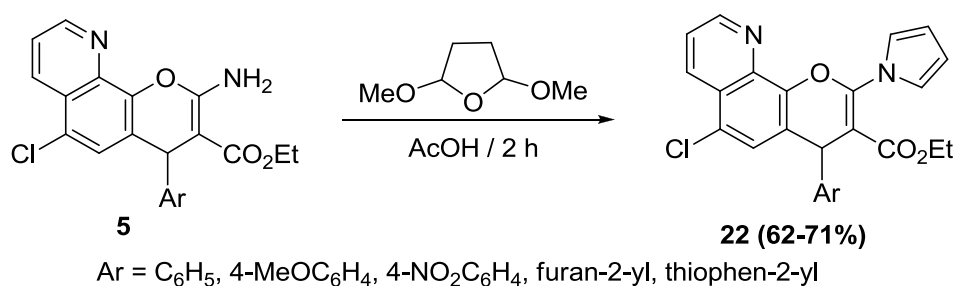
Treatment of the β -enaminonitriles **5** or **7** with ethylenediamine in toluene in the presence of *p*-toluenesulfonic acid under reflux for 12 h yielded the 2-amino-4-aryl-6-chloro/sulfamoyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4*H*-pyrano[3,2-*h*]quinoline derivatives^{36,42,43} (**21**) in 62-78% yield. These reactions were carried out via the nucleophilic addition of the amino group to the protonated ethylenediamine followed by cyclization to give the imidazolyl derivatives (**21**) (Scheme 13).



Scheme 13. Synthetic protocol of 6-chloro/sulfamoyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (**21**)

3-4. Reactions with 2,5-dimethoxytetrahydrofuran

Treatment of the β -enaminoester **5** with 2,5-dimethoxytetrahydrofuran in acetic acid solution under reflux for 2 h afforded ethyl 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline derivatives³⁵ (**22**) in 62-71% yield. This methodology has been achieved through the nucleophilic addition of the amino group to the protonated 2,5-dimethoxytetrahydrofuran followed by cyclization to give the pyrrolyl ester derivatives (**22**) (Scheme 14).



Scheme 14. Synthetic protocol of 6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (**22**)

4. REACTIONS OF 4*H*-PYRANO[3,2-*h*]QUINOLINE DERIVATIVES WITH NUCLEOPHILIC REAGENTS

4-1. Reactions with ammonia and its derivatives

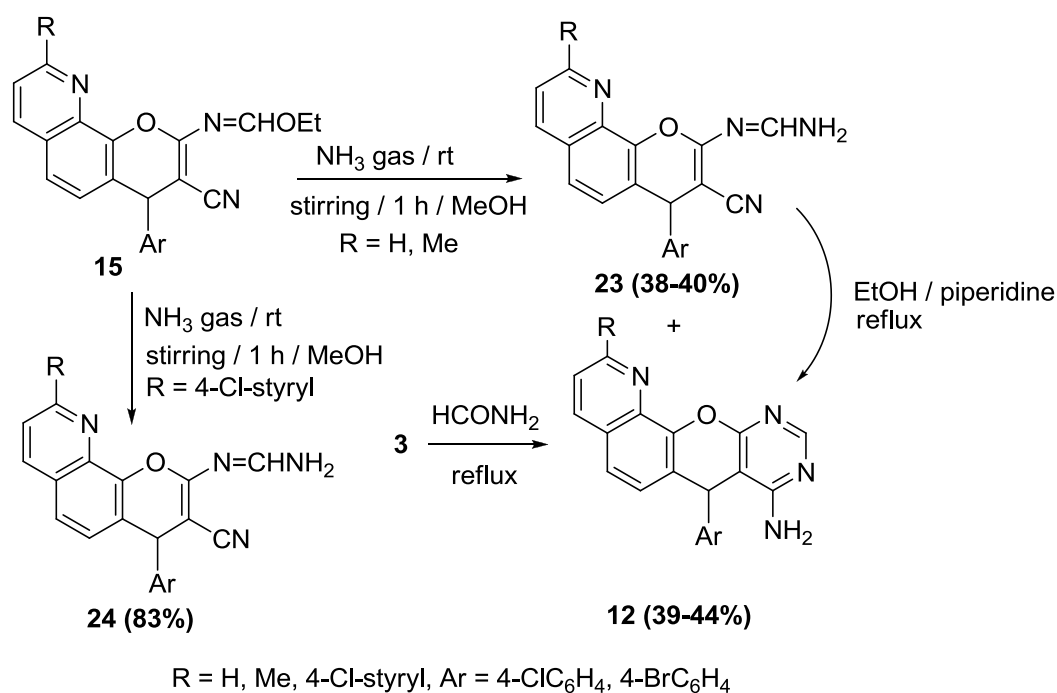
4-1-1. Reactions with ammonia

Treatment of the imidate **15** (R = H, CH₃) with NH₃ gas bubbled in methanol at room temperature for 1 h yielded the 8-amino-7-aryl-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives⁴¹ (**12**) in 39-44% yield, together with the open chain product, 2-aminomethyleneamino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives⁴¹ (**23**) in 38-40% yield (Scheme 15). The open chain product can be separated from the filtrate of the reaction mixture. These reactions were carried out via the nucleophilic addition of

the NH_3 gas to the carbocation of the ethoxymethyleneamino group followed by elimination of EtOH to give the open chain product **23**, or nucleophilic addition of the amino group on the cyano group of **23** followed by cyclization to give the cyclic product **12** respectively.

In a similar manner, reaction of the imidate **15** ($\text{R} = 4\text{-Cl-styryl}$) with NH_3 gas yielded only the open chain product (*E*)-2-aminomethyleneamino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile³⁸ (**24**) in 83% yield (Scheme 15).

The relative *E* configuration of compound **24** was established from the coupling constant values³⁸ ($J = 16$ Hz). The tetracyclic structure **12** was supported by its independent synthesis from the β -enaminonitriles **3** and formamide^{44,45} as described before Scheme 6 and also by cyclization of **23** in ethanolic piperidine solution under reflux⁴⁶ (mp and mixed mp and identical IR and MS spectra) (Scheme 15).

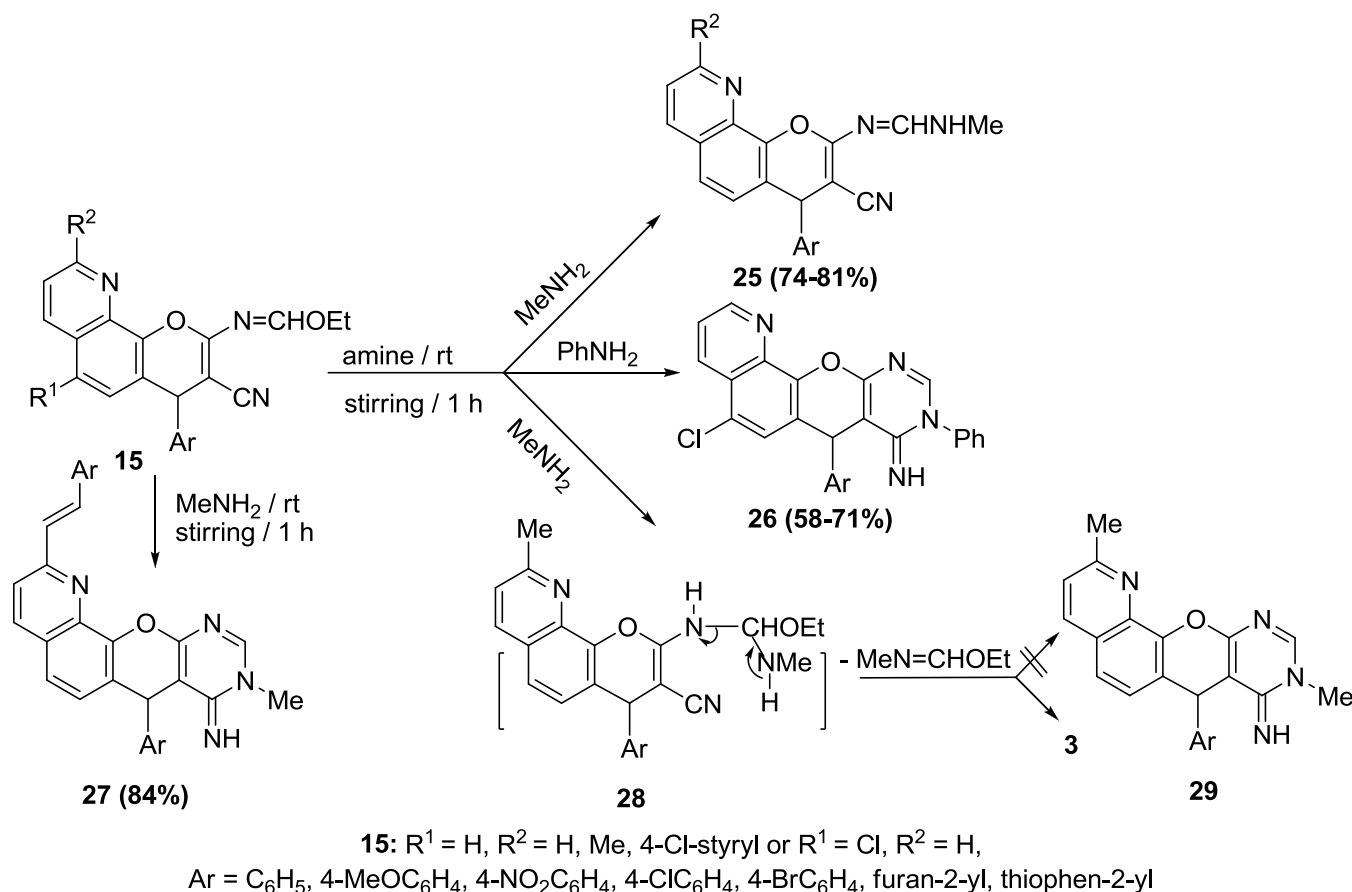


Scheme 15. Synthetic protocol of 8-amino-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline (**12**) and 2-aminomethyleneamino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**23**, **24**)

4-1-2. Reactions with methylamine and aniline

When the imidate **15** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H, Me}$) was treated with methylamine in ethanol at room temperature under stirring for 1 h, the open chain product 4-aryl-2-methylaminomethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives^{40,41} (**25**) ($\text{R}^2 = \text{H, Me}$) was formed in 74-81% yield, rather than the expected cycloaddition compound, imino derivative **27** (Scheme 16), while treatment the imidate **15** ($\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{H}$) with aniline and the imidate **15** ($\text{R}^1 = \text{H}$, $\text{R}^2 = 4\text{-Cl-styryl}$) with methylamine in ethanol at

room temperature under stirring for 1 h, afforded the expected cycloaddition compound, 7-aryl-5-chloro-8-imino-8,9-dihydro-9-phenyl-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives¹² (**26**) in 58-71% yield and (*E*)-9-methyl-7-(4-chlorophenyl)-2-(4-chlorostyryl)-8-imino-8,9-dihydro-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline³⁸ (**27**) in 84% yield, respectively (Scheme 16). The formation of compounds **25-27** was explained according to the explanation described for compounds **12** and **23**.



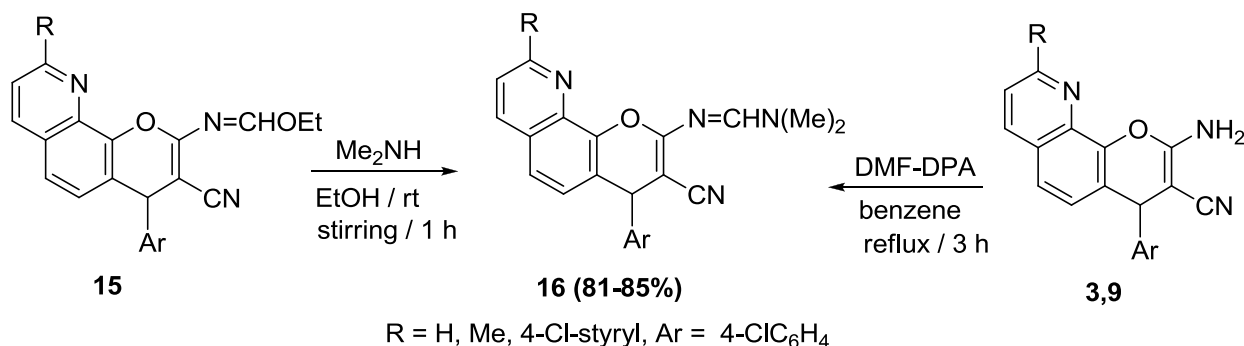
Scheme 16. Reactions of the imidate **15** with different amines

The relative *E* configuration of compound **27** was established from the coupling constant values³⁸ ($J = 16$ Hz). When the imidate **15** ($R^1 = \text{H}, R^2 = \text{Me}$) was treated with methylamine under the same conditions, the addition product **28** was formed and loss ethyl *N*-methylformimidate to give β -enaminonitrile^{46,47} (**3**) ($R^1 = \text{H}, R^2 = \text{Me}$) instead of the imino derivative **29** ($R^1 = \text{H}, R^2 = \text{Me}$) (Scheme 16).

4-1-3. Reactions with dimethylamine

Reaction of the imidate **15** with dimethylamine in ethanol at room temperature under stirring for 1 h afforded the amidine derivative^{38,41} (**16**) in 81-85% yield (Scheme 17), which can be obtained as described before from the reaction of the β -enaminonitriles **3** and **9** with dimethylformamide dipentyl acetal

(DMF-DPA) (mp and mixed mp and identical IR and MS spectra) (Scheme 9). The formation of compound **16** can be explained according to the explanation described for compound **23**.

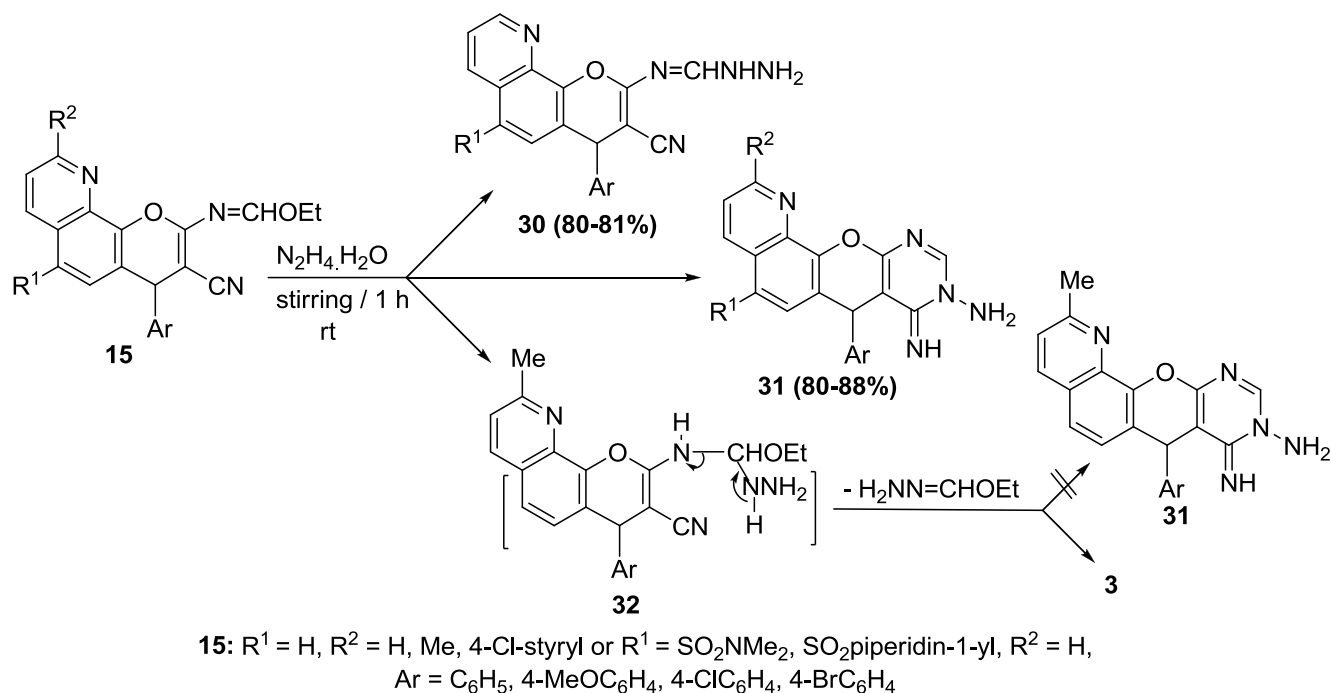


Scheme 17. Reaction of of the imidate **15** with dimethylamine

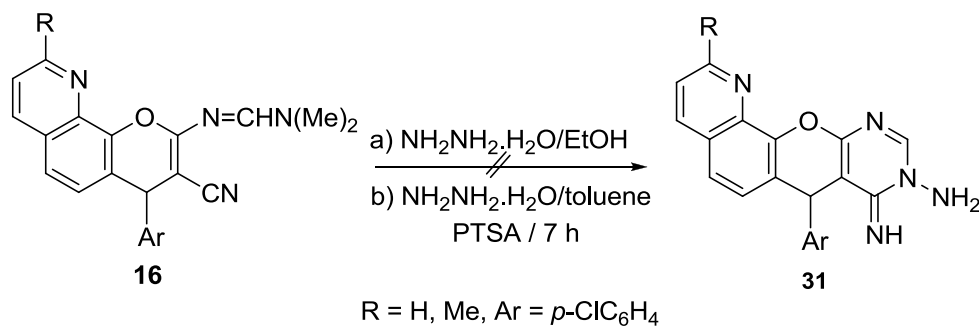
4-1-4. Reactions with hydrazine hydrate

Hydrazinolysis of the imidate **15** ($R^1 = \text{SO}_2\text{NMe}_2$, $\text{SO}_2\text{piperidin-2-yl}$, $R^2 = \text{H}$) in ethanol at room temperature under stirring for 1 h afforded the open chain product 4-aryl-2-hydrazinomethyleneamino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives^{14,41} (**30**) ($R^1 = \text{SO}_2\text{NMe}_2$, $\text{SO}_2\text{piperidin-2-yl}$) in 80-81% yield instead of the cycloaddition product, aminoimino derivative **31** (Scheme 18), while hydrazinolysis of the imidate **15** ($R^1 = \text{H}$, SO_2NMe_2 , $R^2 = \text{H}$, 4-Cl-styryl) under the same conditions yielded the cycloaddition compound, 9-amino-7-aryl-8-imino-8,9-dihydro-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline-5-sulfonamide derivatives³⁸ (**31**) ($R^1 = \text{SO}_2\text{NMe}_2$, $R^2 = \text{H}$) in 80-88% yield and (*E*)-9-amino-7-(4-chlorophenyl)-2-(4-chlorostyryl)-8-imino-8,9-dihydro-7*H*-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline³⁸ (**31**) ($R^1 = \text{H}$, $R^2 = 4\text{-Cl-styryl}$) in 88% yield (Scheme 18). These reactions were carried out via the nucleophilic addition of the amino group of hydrazine hydrate to the carbocation of the ethoxymethyleneamino group followed by elimination of EtOH to give the open chain product **30**, or nucleophilic addition of the imino group on the cyano group of **30** followed by cyclization to give the cyclic product **31** respectively. The relative *E* configuration of compound **31** ($R^1 = \text{H}$, $R^2 = 4\text{-Cl-styryl}$) was established from the coupling constant values³⁸ ($J = 16.5$ Hz).

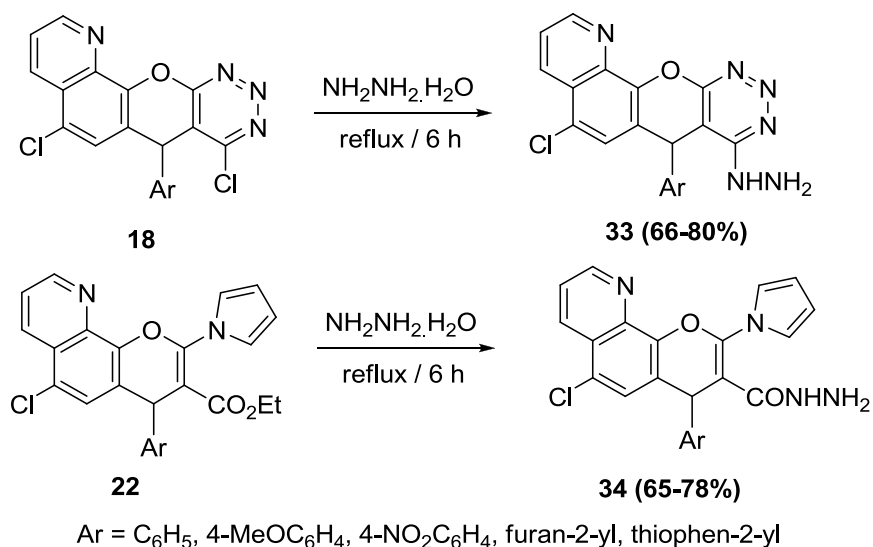
When the imidate **15** ($R = \text{H}$, Me) was treated with hydrazine hydrate in ethanol at room temperature under stirring for 1 h, the addition product **32** was formed and loss ethyl formohydrazone to give the β -enaminonitrile^{46,47} **3** ($R = \text{Me}$) instead of the aminoimino derivative **31** (Scheme 18).

Scheme 18. Hydrazinolysis of the imidate **15**

Hydrazinolysis of the amidine **16** ($R = \text{H, Me}$) in ethanol at room temperature under stirring for 1 h or in toluene/*p*-toluenesulfonic acid under reflux for 7 h was unsuccessful, the aminoimino derivative⁴⁸ **31** ($R = \text{H, Me}$) was not formed (Scheme 19).

Scheme 19. Synthesis of the aminoimino derivative (**31**)

Hydrazinolysis of 5-aryl-4,7-dichloro-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**18**) at reflux for 6 h gave 5-aryl-7-chloro-4-hydrazino-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives³⁶ (**33**) in 66-80% yield (Scheme 20), while hydrazinolysis of the ethyl 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (**22**) under the same conditions, yielded 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbohydrazide³⁵ (**34**) in 65-78% yield, respectively (Scheme 20). The formation of compound **33** proceeded via the nucleophilic substitution reaction, while compound **34** proceeded via the nucleophilic addition reaction respectively.

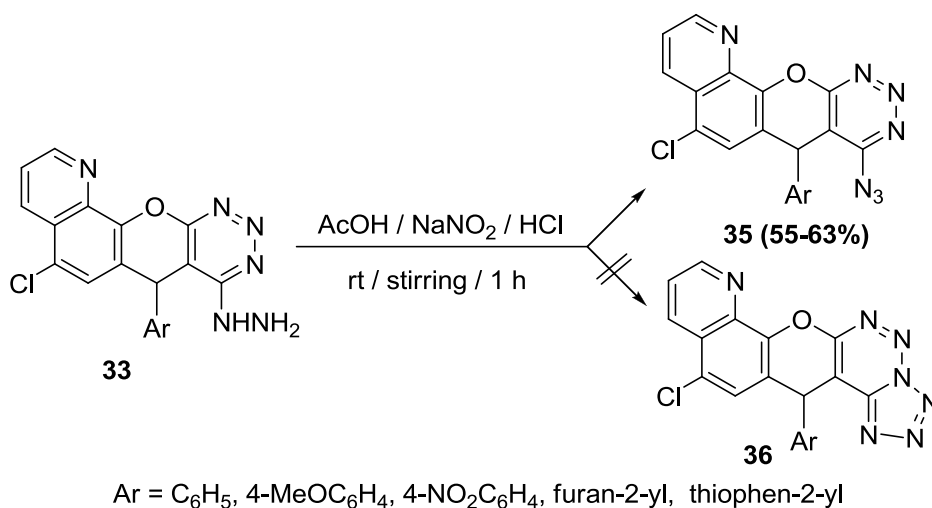


Scheme 20. Hydrazinolysis of 5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**18**) and 2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (**22**)

5. REACTIONS OF 4-HYDRAZINO-5*H*-[1,2,3]TRIAZINO[4',5':6,5]PYRANO[3,2-*h*]-QUINOLINE DERIVATIVES WITH ELECTROPHILIC REAGENTS

5-1. Reactions with sodium nitrite

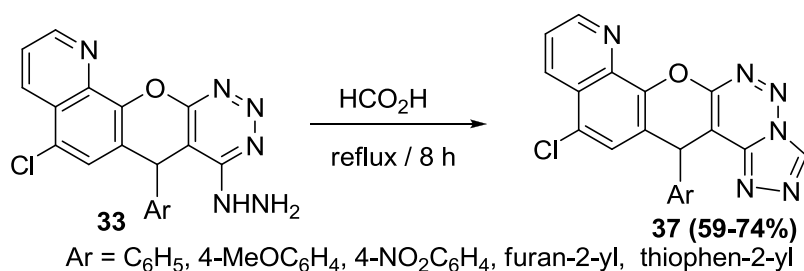
Diazotization of the 5-aryl-7-chloro-4-hydrazino-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**33**) in acetic acid with an aqueous solution of sodium nitrite and hydrochloric acid in ice cold solution under stirring for 1 h led to the formation of the intermediate diazonium salt, which lost HCl to gave 5-aryl-4-azido-7-chloro-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives³⁶ (**35**) in 55-63% yield instead of the tetrazol structure³⁶ (**36**), which ruling out on the basis of spectral data (Scheme 21).



Scheme 21. Synthesis of 4-azido-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**35**)

5-2. Reactions with formic acid

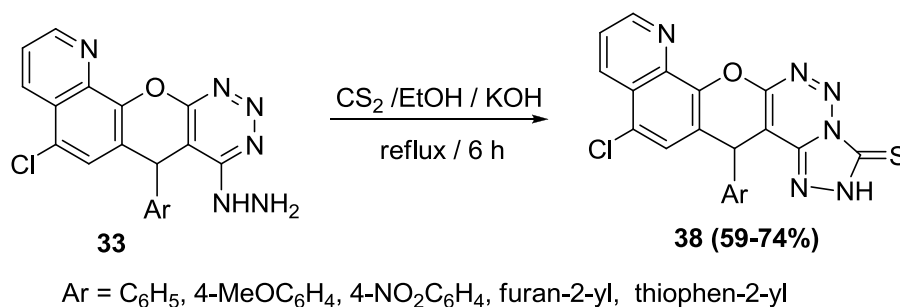
Condensation of 5-aryl-7-chloro-4-hydrazino-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**33**) with formic acid under reflux for 8 h gave the corresponding 14-aryl-12-chloro-14*H*-[1,2,4]triazolo[3,4-*f*][1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives³⁶ (**37**) in 59-74% yield (Scheme 22). The formation of compound **37** proceeded via the nucleophilic addition of the amino group of hydrazino group to the carbocation of the formic acid followed by rearrangement and cyclization with elimination of H₂O to give compound **37**.



Scheme 22. Synthesis of 14*H*-[1,2,4]triazolo[3,4-*f*][1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**37**)

5-3. Reactions with carbon disulfide

Treatment of 5-aryl-7-chloro-4-hydrazino-5*H*-[1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives (**33**) with carbon disulfide/KOH in ethanol under reflux for 6 h gave the corresponding 14-aryl-12-chloro-3-thioxo-14*H*-[1,2,4]triazolo[3,4-*f*][1,2,3]triazino[4',5':6,5]pyrano[3,2-*h*]quinoline derivatives³⁶ (**38**) in 59-74% yield (Scheme 23). The reaction proceeded by nucleophilic addition of the amino group of hydrazino group to the carbocation of the carbon disulfide followed by rearrangement and cyclization with elimination of H₂S to give compound **38**.

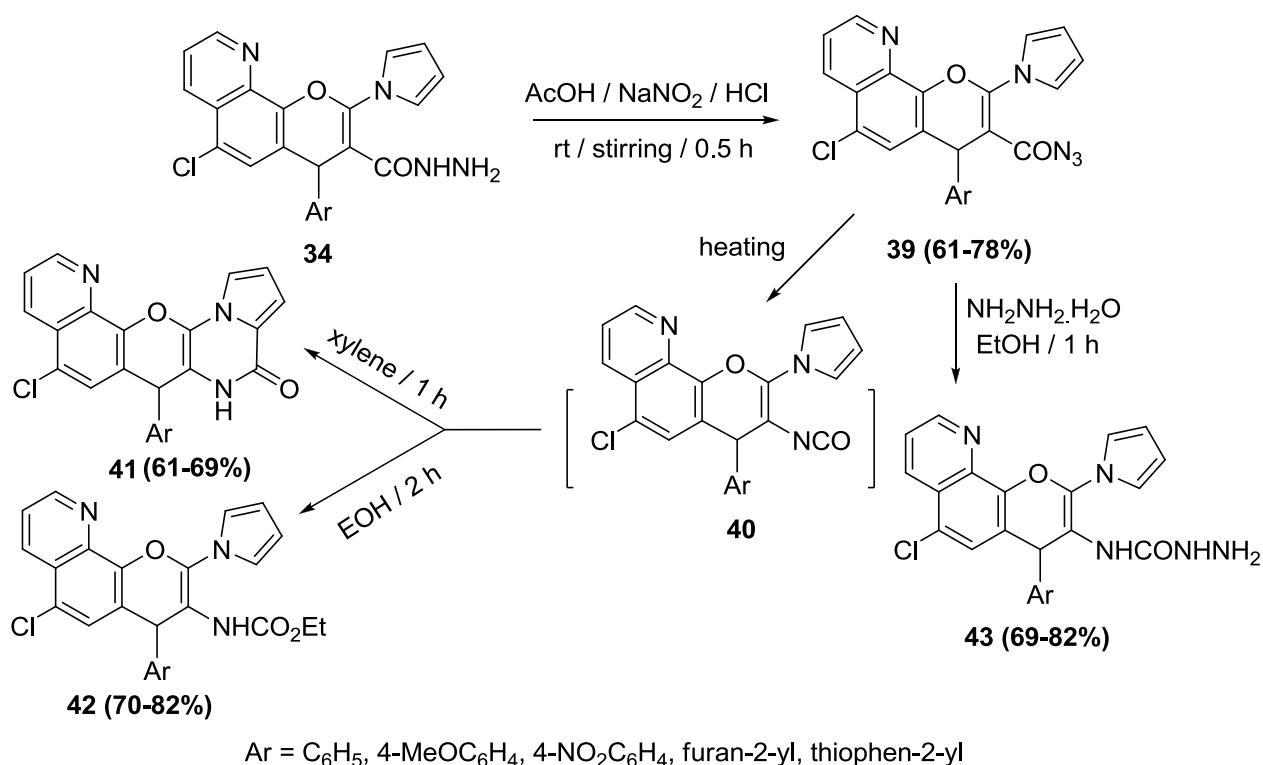


Scheme 23. Synthesis of 3-thioxo-14*H*-[1,2,4]triazolo[3,4-*f*][1,2,3]-triazino[4',5':6,5]pyrano[3,2-*h*]-quinolines (**38**)

6. REACTIONS OF 4*H*-PYRANO[3,2-*h*]QUINOLINE-3-CARBOHYDRAZIDE DERIVATIVES WITH ELECTROPHILIC REAGENTS

6-1. Reactions with sodium nitrite

Diazotization of the 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbohydrazide (**34**) in acetic acid with an aqueous solution of sodium nitrite and hydrochloric acid in ice cold solution under stirring for 0.5 h gave 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline-3-oylazine³⁵ (**39**) in 61-78% yield (Scheme 24). The formation of compound **39** can be explained according to the explanation described for compound **35**.



Scheme 24. Synthetic protocol of compounds (**39**) and (**41-43**)

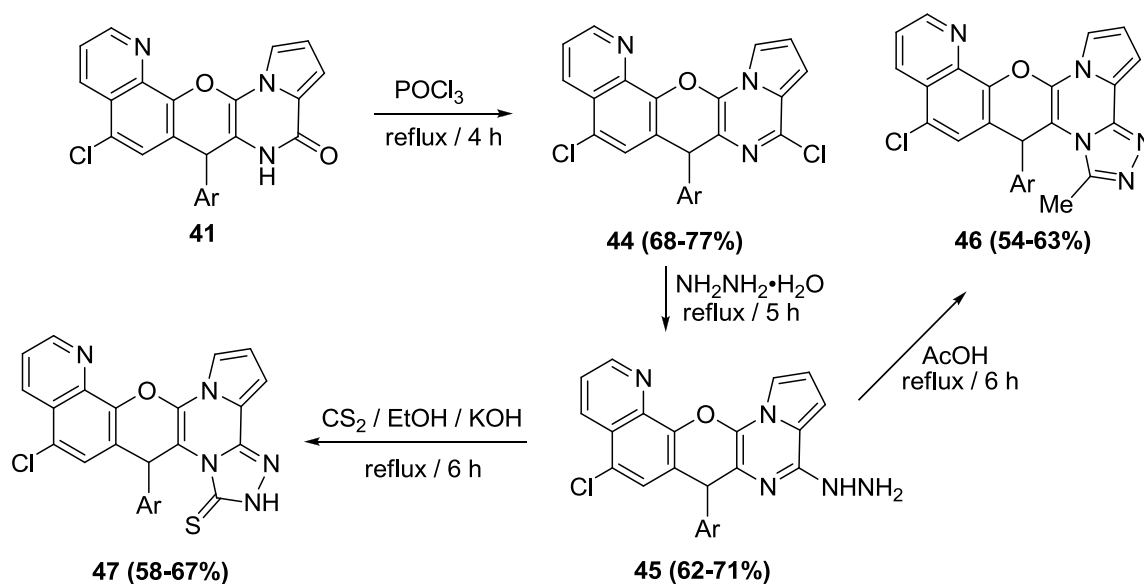
When the acid azide **39** was heated in a high-boiling point inert solvent such as xylene led to Curtius rearrangement with concomitant ring closure of the isocyanate intermediate **40** giving 7-aryl-5-chloro-9-oxo-7*H*-8,9-dihydropyrrolyl[1'',2'':1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives³⁵ (**41**) in 61-69% yield, while heating the acid azide **39** in excess ethanol for 2 h afforded the ethyl 4-aryl-6-chloro-2-(1-pyrrolyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbamate derivatives³⁵ (**42**) in 70-82% yield (Scheme 24).

Hydrazinolysis of the acid azide **39** in ethanol under reflux for 1 h afforded *N*-(4-aryl-6-chloro-2-(1*H*-pyrrol-1-yl)-4*H*-pyrano[3,2-*h*]quinolin-3-yl)hydrazinecarboxamide³⁵ (**43**) in 69-82% yield (Scheme 24).

7. REACTIONS OF 7*H*-DIHYDROPYRROLYL[1'',2'':1',2']PYRAZINO-[5,6:5',6']PYRANO[3,2-*h*]QUINOLINE DERIVATIVES

Chlorination of the 7-aryl-5-chloro-9-oxo-7*H*-8,9-dihydropyrrolyl[1'',2'':1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives (**41**) with phosphorus oxytrichloride under reflux for 4 h gave 7-aryl-5,9-

dichloro-7*H*-pyrrolo[1",2":1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives³⁵ (**44**) in 68-77% yield (Scheme 25). Hydrazinolysis of **44** with hydrazine hydrate in ethanol under reflux for 5 h gave 7-aryl-5-chloro-9-hydrazino-7*H*-pyrrolo[1",2":1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives³⁵ (**45**) in 62-71% yield (Scheme 25). Treatment of **45** with acetic acid under reflux for 6 h gave 7-aryl-5-chloro-9-methyl-7*H*-[1,2,4]triazolo[3",4":3',4']pyrrolo[1",2":1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives³⁵ (**46**) in 54-63% yield, while reaction of **45** with carbon disulfide / KOH in ethanol under reflux for 6 h gave 7-aryl-5-chloro-9-thioxo-9,10-dihydro-7*H*-[1,2,4]triazolo[3",4":3',4']pyrrolo[1",2":1',2']pyrazino[5,6:5',6']pyrano[3,2-*h*]quinoline derivatives³⁵ (**47**) in 58-67% yield (Scheme 25). The formation of compound **45** proceeded via the nucleophilic substitution reaction, while compounds **46** and **47** were formed via nucleophilic addition of the amino group of hydrazino group to the AcOH or CS₂ followed by elimination of H₂O or H₂S to give **46** and **47** respectively.

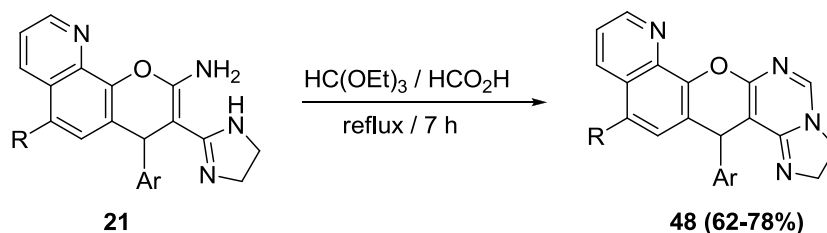


Scheme 25. Synthetic protocol of compounds (**44-47**)

8. REACTIONS OF DIHYDRO-1*H*-IMIDAZOL-2-YL-4*H*-PYRANO[3,2-*h*]QUINOLINE DERIVATIVES WITH ELECTROPHILIC REAGENTS

8-1. Reactions with triethyl orthoformate

Interaction of 2-amino-4-aryl-6-chloro/sulfamoyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (**21**) with triethyl orthoformate in formic acid under reflux for 7 h gave the 14-aryl-12-chloro/sulfamoyl-2,3-dihydroimidazo[1,2-*c*]pyrimido[4',5':6,5]-14*H*-pyrano[3,2-*h*]quinoline derivatives^{36,49} (**48**) in 62-78% yield (Scheme 26) through the loss of 2 EtOH molecules to give the intermediate ethoxymethyleneamino derivative which cyclized with imino group of 1*H*-imidazoly ring to afford the compound **48**.

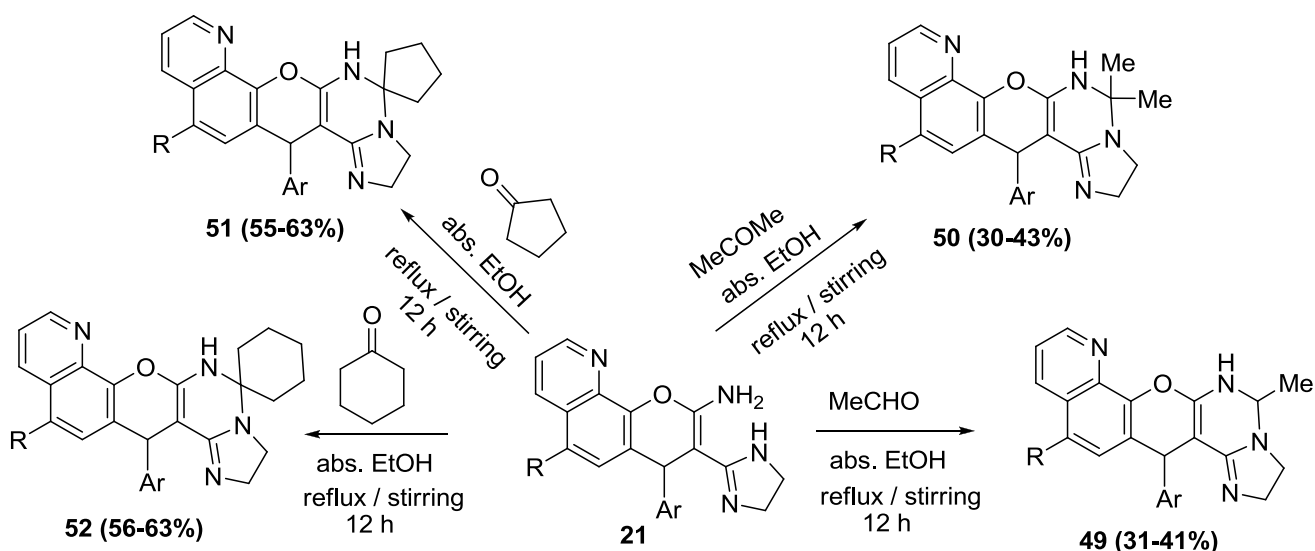


R = Cl, SO₂NMe₂, Ar = C₆H₅, 4-MeOC₆H₄, 4-NO₂C₆H₄, furan-2-yl, thiophen-2-yl

Scheme 26. 12-chloro/sulfamoyl-2,3-dihydroimidazo[1,2-*c*]pyrimido[4',5':6,5]-14*H*-pyrano[3,2-*h*]-quinoline derivatives (**48**)

8-2. Reactions with carbonyl compounds

Condensation of 2-amino-4-aryl-6-chloro/sulfamoyl-3-(4,5-dihydro-1*H*-imidazol-2-yl)-4*H*-pyrano-[3,2-*h*]quinoline derivatives (**21**) with carbonyl compounds, namely, acetaldehyde, acetone, cyclopentanone and cyclohexanone in absolute ethanol under stirring and reflux at 80-100 °C for 12 h afforded 14-aryl-12-chloro/sulfamoyl-2,3,6-trihydroimidazo[1,2-*c*]pyrimido[4',5':6,5]-14*H*-pyrano[3,2-*h*]quinoline derivatives [16,29](#) (**49-52**) in 30-63% yield, respectively (Scheme 27). These reactions were carried out via the nucleophilic addition of the amino group to the carbocation of the carbonyl compounds with elimination of H₂O followed by cyclization of imino group of 1*H*-imidazoly ring with benzylideneamino group (-N=CHR) to afforded the compounds **49-52**.



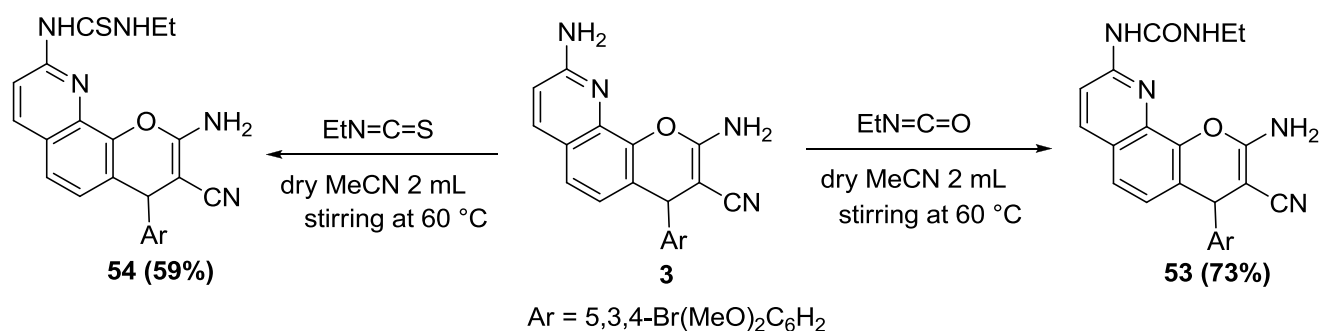
R = Cl, SO₂NMe₂, Ar = C₆H₅, 4-MeOC₆H₄, 4-NO₂C₆H₄, furan-2-yl, thiophen-2-yl

Scheme 27. Synthetic protocol of compounds (**49-52**)

9. Reactions of 2,9-diamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile with electrophilic reagents

9-1. Reactions with ethyl isocyanate or ethyl thioisocyanate

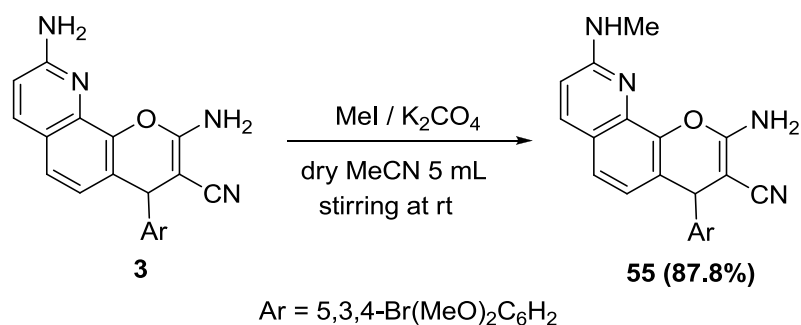
2,9-Diamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**3**) and ethyl isocyanate or ethyl thioisocyanate were taken in 2 mL dry acetonitrile and stirred at 60 °C monitoring the reaction with LC-MS. The solvent was evaporated after the completion of the reaction. The residue was separated on HPLC (high performance liquid chromatography) (21 mm x 250 mm, RP18, 5 mm) with a methanol/water gradient (5% MeOH to MeOH in 25 min, flow 21 mL/min) to afford 1-(2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4*H*-pyrano[3,2-*h*]quinolin-9-yl)-3-methylurea³⁹ (**53**) and 1-(2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4*H*-pyrano[3,2-*h*]quinolin-9-yl)-3-methylthiourea³⁹ (**54**) in 59-73% yield, respectively (Scheme 28). The reaction proceeded by nucleophilic addition of the amino group to the carbocation of ethyl isocyanate or ethyl thioisocyanate followed by rearrangement to gave compounds **53** and **54**.



Scheme 28. Synthesis of urea and thiourea derivatives (**53**, **54**)

9-2. Reactions with iodomethane

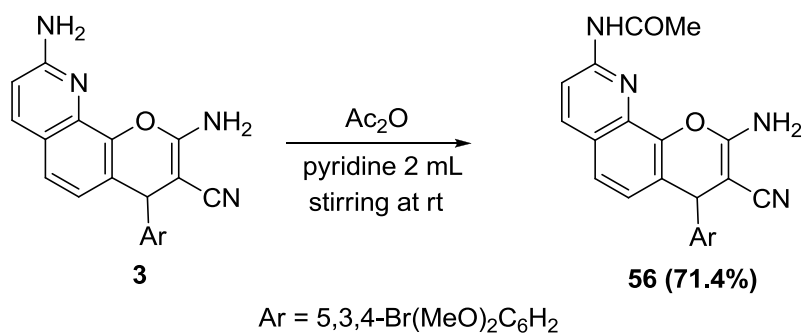
2,9-Diamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**3**) and potassium carbonate were taken in 5 mL dry acetonitrile, charged with iodomethane and stirred at room temperature monitoring the reaction with LC-MS. The solvent was evaporated after the completion of the reaction. The residue was separated on HPLC (21 mm x 250 mm, RP18, 5 mm) with a methanol/water gradient (5% MeOH to MeOH in 25 min, flow 21 mL/min) to afford 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-9-(methylamino)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile³⁹ (**55**) in 87.8% yield (Scheme 29). The formation of compound **55** was explained via the nucleophilic addition of the amino group to the carbocation of the iodomethane to give compound **55**.



Scheme 29. Synthesis of 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-9-(methylamino)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**55**)

9-3. Reactions with acetic anhydride

2,9-Diamino-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**3**) was taken in 2 mL pyridine at 0 °C, charged with acetic anhydride by dropwise addition and stirred at room temperature monitoring the reaction with LC-MS. The solvent was evaporated after the completion of the reaction. The residue was separated on HPLC (21 mm x 250 mm, RP18, 5 mm) with a methanol/water gradient (5% MeOH to MeOH in 25 min, flow 21 mL/min) to get the title compound, *N*-(2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4*H*-pyrano[3,2-*h*]quinolin-9-yl)acetamide³⁹ (**56**) in 71.4% yield (Scheme 30). Acylation of compound **56** can be explained according to the explanation described for compound **13**.

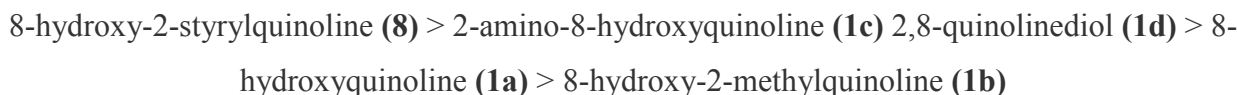


Scheme 30. Synthesis of *N*-(2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-4*H*-pyrano[3,2-*h*]quinolin-9-yl)acetamide (**56**)

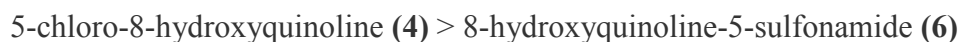
10. CONCLUSION

The present review outlined the synthesis of 4*H*-pyrano[3,2-*h*]quinoline derivatives by reaction of 8-hydroxyquinoline and its derivatives with α -cyanocinnamionitriles and ethyl α -cyanocinnamates, fused 4*H*-pyrano[3,2-*h*]quinoline derivatives by treatment of 4*H*-pyrano[3,2-*h*]quinoline derivatives with different electrophilic followed by nucleophilic reagents and heterocyclic ring transformations. The tendency of the 8-hydroxyquinoline, 2-substituted 8-hydroxyquinoline (**1a-d**) and 8-hydroxy-2-styryl-

quinoline (**8**) towards the electrophilic β -carbon of α -cyanocinnamitriles and ethyl α -cyanocinnamates illustrated that the order of reactivity of 8-hydroxyquinoline and its derivatives follows the following sequence:



In addition, the tendency of the 5-chloro-8-hydroxyquinoline (**4**) and 8-hydroxyquinoline-5-sulfonamide (**6**) towards the electrophilic β -carbon of α -cyanocinnamitriles illustrated that the order of reactivity of 5-substituted 8-hydroxyquinolines follow the following sequence:



This can be explained through the mesomeric effect between the quinoline-*N* and the hydroxyl group in the 8-position, the conjugation effect, resonance effect and inductive effect between different substituent groups at 2-position and 5-position and the quinoline ring.

The investigation of antimicrobial and antitumor screening data for the synthesis compounds revealed that some of the tested compounds have demonstrated congruent activities against the most tested microorganisms and human tumor cell lines as compared with the standard drugs.

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