Synthesis of certain novel 4*H*-pyrano[3,2-*h*]quinoline derivatives

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Abstract

Treatment of 8-hydroxyquinoline **1a** and 8-hydroxy-2-methylquinoline **1b** with *α*-cyano-*p*-chloro/bromocinnamonitriles **2a,b** provided 4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives **3a-d**, while treatment of *(E)* 2-(4-chlorostyryl)-8-hydroxyquinoline **7** with *α*-cyano-*p*-chloro/bromocinnamonitriles **2a,b** and ethyl *α*-cyano-*p*-chloro/bromocinnamates **2d,e** provided 4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives **8a,b** and ethyl 4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate derivatives **9a,b** respectively. Interaction of 8-hydroxyquinoline **1a** and 8-hydroxy-2-methylquinoline **1b** with *α*-cyano-*p*-fluorocinnamonitrile **2c** afforded 2-[4-(piperidin-1-yl)benzylidene]malononitrile **5** via a nucleophilic aromatic substitution reaction. The reactivity of 2-hydroxyquinoline and its 2-substituted derivatives towards *α*-cyano-*p*-chloro/bromocinnamonitriles and ethyl *α*-cyano-*p*-chloro/bromocinnamates are discussed in this work. Structures of these compounds were established on the basis of IR, ^{1}H NMR, ^{13}C NMR, ^{13}C NMR-DEPT and MS data.

Keywords: 8-Hydroxyquinoline, 8-hydroxy-2-methylquinoline, *(E)* 2-(4-chlorostyryl)-8-hydroxyquinoline, *α*-cyano-*p*-halocinnamonitriles/ethyl *α*-cyano-*p*-halocinnamates, 4*H*-pyrano-[3,2-*h*]quinoline derivatives, 2-[4-(piperidin-1-yl)benzylidene]malononitrile

Introduction

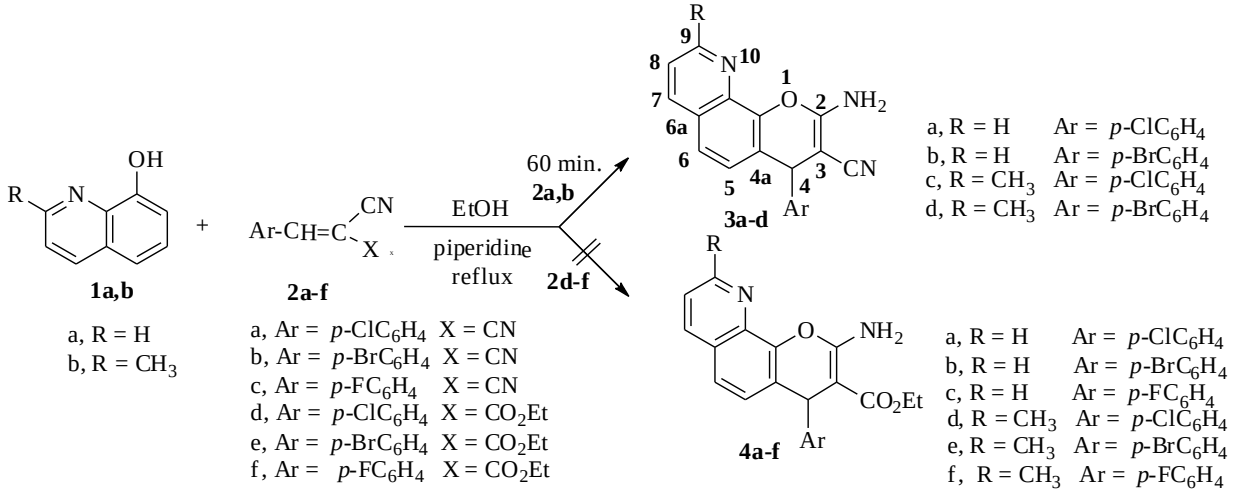
Quinoline moiety is present in many classes of biologically active compounds [1]. The biological activity of these quinoline derivatives depends not only on the bicyclic hetero-aromatic pharmacophore but also on the nature of the peripheral substituent and their spatial relationship. They also exhibit antimalarial [2], antitumor [3], antioxidant [4], antileishmanial [5] and antiplatelet activities [6]. In addition they function as pharmacologically active synthetic compounds [7] such as DNA binding capabilities [8] and DNA-intercalating carrier [9]. A series of compounds derived from 8-hydroxyquinoline as potential HIV-1 integrate inhibitors were synthesized recently [10]. In

addition styrylquinoline derivatives have gained strong attention recently due to their activities as perspective HIV integrase inhibitors [11] and also, for their extensive biological activities.[1b-d, 11c]

In continuation of the previous works [12-26], it seemed interesting to synthesize new 4*H*-pyrano[3,2-*h*]quinoline derivatives by using *α*-cyano-*p*-halocinnamonitriles and ethyl *α*-cyano-*p*-halocinnamates and evaluatation of their antimicrobial and antitumor activities. The observation of the reactivity of 2-hydroxyquinoline and its 2-substitued derivatives towards *α*-cyano-*p*-halocinnamonitriles and ethyl *α*-cyano-*p*-halocinnamates are discussed in this work.

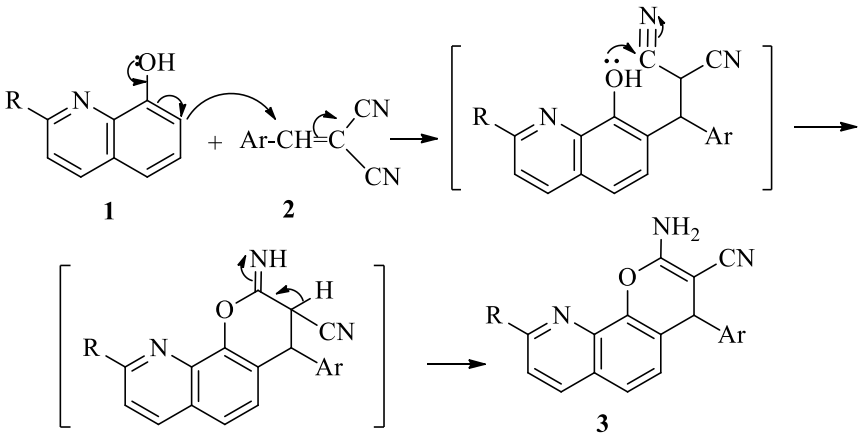
Results and Discussion

Treatment of 8-hydroxyquinoline **1a** and 8-hydroxy-2-methylquinoline **1b** with *α*-cyano-*p*-chloro/bromocinnamonitrile **2a,b** in ethanolic piperidine under reflux afforded 2-amino-4-(4-chloro/bromophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3a,b** and 2-amino-4-(4-chloro-/bromophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3c,d**, while treatment of **1a,b** with ethyl *α*-cyano-*p*-chloro/bromo/fluorocinnamate **2d-f** in ethanolic piperidine under reflux were unsuccessful, ethyl 2-amino-4-(4-halophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate **4a-c** and 2-amino-4-(4-halophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate **4d-f** were not formed [27] (Scheme 1).



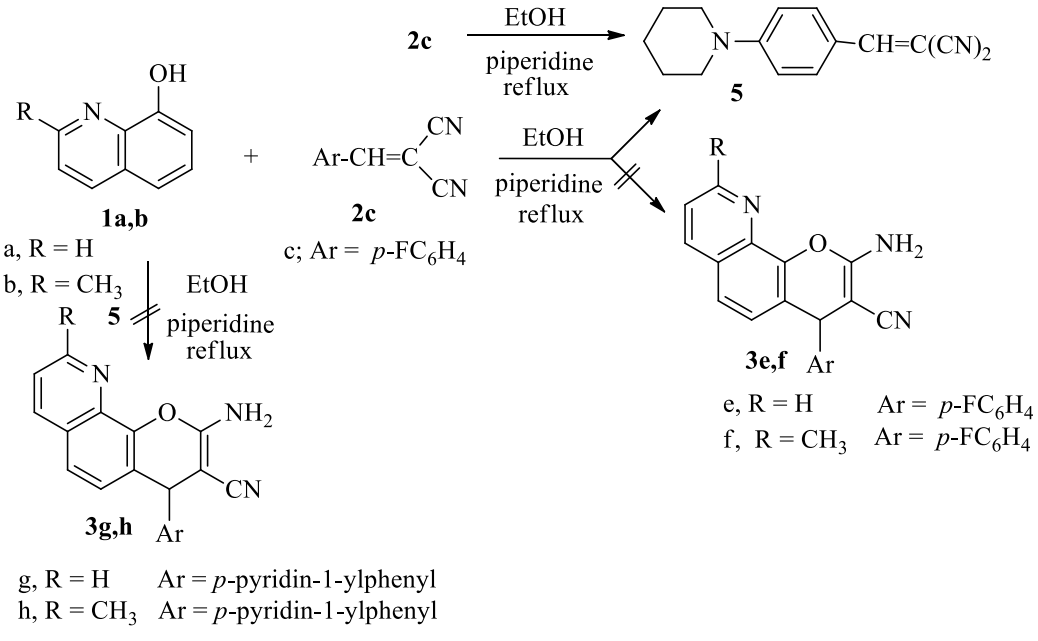
Scheme 1. Synthesis of 4*H*-pyrano[3,2-h]quinoline derivatives **3a-d.**

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



Scheme 2. Mechanism formation of compounds **3.**

Furthermore, reaction of **1a,b** with *α*-cyano-*p*-fluorocinnamonitrile **2c** afforded 2-[4-(piperidin-1-yl)benzylidene]malononitrile **5** instead of the formation of 2-amino-4-(4-fluorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3e** and the 2-amino-4-(4-fluorophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3f**. In the case of compound 5 the fluorine atom of **2c** had simply been displaced by piperidine [28-31] via a nucleophilic aromatic substitution reaction (Scheme 3). Attempts to react **1a,b** with **5** was unsuccessful, 2-amino-4-(4-piperidin-1-ylphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3g** and 2-amino-4-(4-piperidin-1-ylphenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **3h** were not formed [28] (Scheme 3).



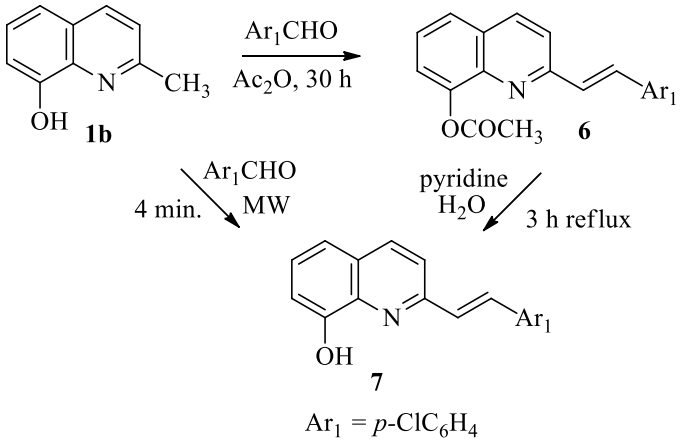
Scheme 3. Synthesis of 2-[4-(piperidin-1-yl)-benzylidene]malononitrile.

Structure of **5** was also supported by an independent synthesis of the same compound by nucleophilic substitution of the fluorine atom of **2c** with piperidine [28] in ethanol under reflux (m.p. and mixed m.p.) (Scheme 3).

Structure **3** was established on the basis of spectral data. The IR spectra of **3a-d** showed the presence of a NH_2 stretch at υ 3464-3395, 3344-3310 cm^{-1} and a CN stretch at υ 2196-2188 cm^{-1}. NMR spectra of **3a-d** showed characteristic signals for 4*H*-pyran: singlets at δ 4.98-4.82 ppm in the ^1H NMR and 41.51-40.46 ppm in the ^{13}C NMR. The mass spectra of compounds **3a-d** gave additional evidences for the proposed structures.

Condensation of 8-hydroxy-2-methylquinoline **1b** with *p*-chlorobenzaldehyde in acetic anhydride under reflux give *(E)* 2-(4-chlorostyryl)-8-hydroxyquinoline **7** via the intermediate *(E)* 8-acetoxy-2-(4-chlorostyryl)quinoline **6**, while condensation of **1b** with *p*-chlorobenzaldehyde under Microwave irradiation furnished **7** [1f,g] (Scheme 4).

The relative *(E)* configuration of compounds **6** and **7** were established from the coupling constant values (J = 17 Hz) for **6** and (J = 16 Hz) for **7**.



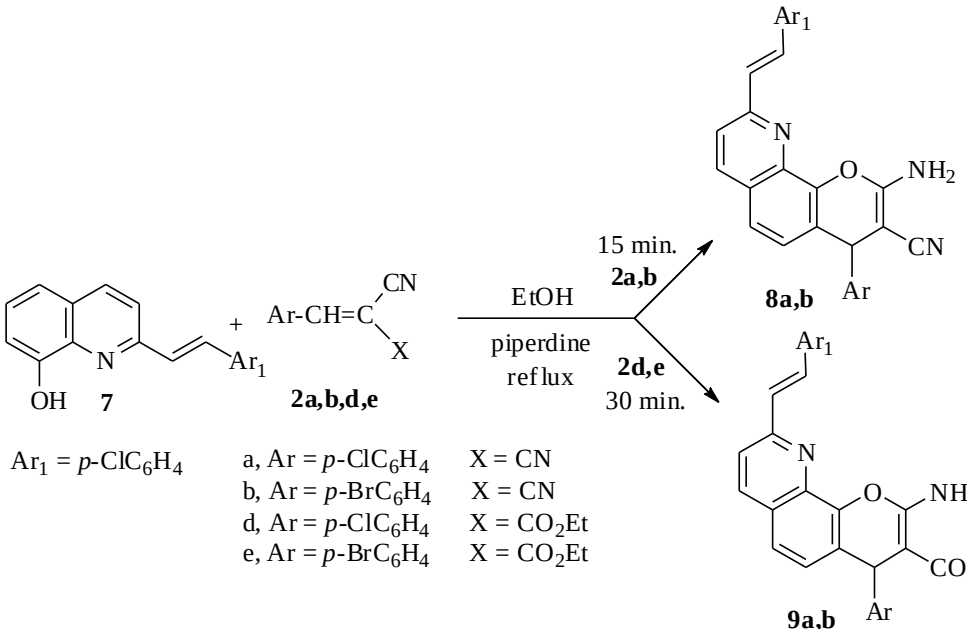
Scheme 4. Preparation of (*E*) 8-acetoxy-2-(4-chlorostyryl)quinoline **6** and (*E*) 8-hydroxy-2-(4-chlorostyryl)quinoline **7.**

The structures of **6** and **7** were established on the basis of spectral data. The IR spectra of **6** showed the presence of a CO stretch at υ 1760 cm,$^{-1}$ while for **7** showed the appearance of a OH stretch at υ 3349 cm.$^{-1}$ The ^1H and ^{13}C NMR spectra of **6** revealed the presence of signals at δ 7.63 (d, J = 17 Hz, 1H, =CH), 7.47 (d, J = 17 Hz, 1H, =CH), 2.60 ppm (s, 3H, $COCH_3$) and 134.42 (=CH), 129.35 (=CH), 21.06 ppm (CH_3). The ^{13}C NMR-DEPT spectrum at 45°, 90° and 135° of **6** provided additional evidence in support of the proposed structure. The ^{13} C NMR-DEPT spectrum of **6** at δ 135^o CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δ 134.42 (=CH ↑), 129.35 (=CH ↑), 21.06 (CH_3 ↑), while at 90° only CH signals are positive (up) and showed at δ 134.42 (=CH ↑), 129.35 (=CH ↑) and at 45° (CH, CH_2 and CH_3 positive) revealed signals at δ 134.42 (=CH ↑), 129.35 (=CH ↑), 21.06 (CH_3 ↑). Characteristic resonances were observed at δ 9.85 (bs, 1H, OH), 8.14 (d, J = 16 Hz, 1H, =CH),

7.51 ppm (d, *J* = 16 Hz, 1H, =CH) and 135.15 (=CH), 131.62 ppm (=CH) for **7**. The mass spectra of compounds **6** and **7** gave additional evidences for the proposed structures.

Treatment of *(E)* 2-(4-chlorostyryl)-8-hydroxyquinoline **7** with **2a,b,d,e** in ethanolic piperidine under reflux afforded *(E)* 2-amino-4-(4-chloro/bromophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile **8a,b** and ethyl *(E)* 2-amino-4-(4-chloro/bromophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate **9a,b** respectively (Scheme 5).

The relative *(E)* configuration of compounds **8** and **9** were established from the coupling constant values (*J* = 16.5 Hz) for **8a,9a** and (*J* = 16 Hz) for **8b,9b**.

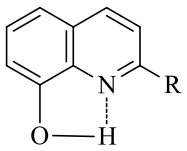


Scheme 5. Synthesis of 9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline derivatives **8a,b** and **9a,b.**

The structures **8** and **9** were established on the basis of spectral data. The IR spectra of **8a,b** showed the appearance of the a NH_2 stretch at υ 3417-3384, 3315-3310, 3199-3182 cm,$^{-1}$ a CN stretch at υ 2198-2189 cm,$^{-1}$ while a NH_2 stretch at υ 3409-3380, 3349**-**3296 cm^{-1} and a CO stretch at υ 1677-1643 cm^{-1} for **9a,b**. The ^{1}H and ^{13} C NMR spectra of **8a,b** and **9a,b** revealed the presence of 4*H* signals at δ 5.09-5.00 (s, 1H, H-4) and 40.71-40.09 ppm (C-4). In compounds **9a,b** the ester group gave ^{1}H signals at 4.13-4.01 (q, *J* = 7 Hz, 2H, CH_2), 1.22-1.10 (t, *J* = 7 Hz, 3H, CH_3) with the corresponding signals in the ^{13}C spectra at δ 59.59-58.75 (CH_2) and 14.39-14.27 ppm (CH_3) respectively. The ^{13}C NMR-DEPT spectra at 45°, 90° and 135° of compounds **8a,b** provided additional evidence in support of the proposed structures. Also,t he mass spectra of compounds **8** and **9** gave additional evidences for the proposed structures.

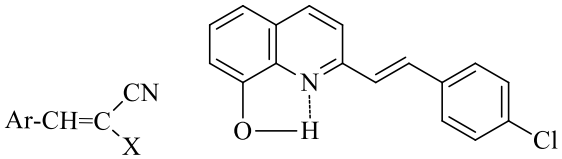
From the experimental observations (reaction time and yield), the authors pointed out that, the tendency of the 8-hydroxyquinoline **1a** and 2-substituted-8-hydroxyquinoline **1b,7** towards

the electrophilic *β*-carbon of *α*-cyano-*p*-chloro/bromocinnamonitriles **2a,b** and ethyl *α*-cyano-*p*-chloro/bromocinnamates **2d,e** follows the following sequence:



8-Hydroxy-2-styrylquinoline > 8-hydroxyquinoline > 8-hydroxy-2-methylquinoline

Thus, the reactivity was enhanced with the presence of the styryl group in the 2-position and deactivated with the methyl group in the 2-position and this was explained through the mesomeric effect between the quinoline-*N* and the hydroxyl group in the 8-position as shown in (Scheme 6).



2a,b,d,e **7**

a, Ar = *p*-ClC_6H_4 X = CN
b, Ar = *p*-BrC_6H_4 X = CN
d, Ar = *p*-ClC_6H_4 X = CO_2Et
e, Ar = *p*-BrC_6H_4 X = CO_2Et

Scheme 6. The reactivity of (*E*) 2-(4-chlorostyryl)-8-hydroxyquinoline **7.**

Also, this observation was supported by the easy attacks of phenolate anion (C-7) of **7** at the *β*-carbon of ethyl *α*-cyano-*p*-chloro/bromocinnamates **2d,e** rather than **1a** and **1b** to yield an acyclic Michael adduct, which underwent cyclization to give **9**.

Conclusions

In this paper we report the synthesis of some 4*H*-pyrano[3,2-*h*]quinoline derivatives **3a-d, 8a,b** and **9a,b** via interaction of 8-hydroxyquinoline **1a** and 2-substituted-8-hydroxyquinoline **1b,7** with *α*-cyano-*p*-chloro/bromocinnamonitriles **2a,b** and ethyl *α*-cyano-*p*-chloro/bromocinnamates **2d,e**. The tendency of the 8-hydroxyquinoline and 2-substituted-8-hydroxyquinoline towards the electrophilic *β*-carbon of *α*-cyano-*p*-chloro/bromocinnamonitriles and ethyl *α*-cyano-*p*-chloro/bromocinnamates illustrated that the order of reactivity of 8-hydroxyquinoline **1a** and 2-substituted-8-hydroxyquinoline **1b,7** follows the following sequence:

8-Hydroxy-2-styrylquinoline > 8-hydroxyquinoline > 8-hydroxy-2-methylquinoline

This is can be explained through the mesomeric effect between the quinoline-*N* and the hydroxyl group in the 8-position.

Experimental Section

General. Melting points were determined with a Stuart Scientific Co. Ltd apparatus. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on using a Bruker AV 500 MHz spectrometer using tetramethylsilane (TMS) as an internal reference and results are expressed as δ (ppm) values. ^{13}C NMR spectra were obtained using distortionless enhancement by polarization transfer (DEPT), with this technique, the signals of CH & CH_3 carbon atoms appears normal (up) and the signal of carbon atoms in CH_2 environments appears negative (down). The MS were measured on a Shimadzu GC/MS-QP5050A spectrometer. Elemental analyses for C, H and N were performed on a Perkin-Elmer 240 microanalyser in the Faculty of Science Cairo University.

General procedure for the preparation of 4*H*-pyrano[3,2-*h*]quinoline derivatives (3a-d) and 2-[4-(piperidin-1-yl)benzylidene]malononitrile (5)

A solution of 8-hydroxyquinoline **1a** or 8-hydroxy-2-methylquinoline **1b** (0.01 mmol) in EtOH (30 ml) was treated with *α*-cyano-*p*-chloro/bromo/fluorocinnamonitriles **2a-c** (0.01 mmol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation occurred (reaction times: 60 min.). The solid product which formed was collected by filtration and recrystallised from benzene for compounds **3a-d** and from ethanol for compound **5**. The physical and spectral data of compounds **3a-d** and **5** are as follows:

2-Amino-4-(4-chlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3a). Buff needles, yield 83%, m.p. 249-250 ºC; [Lit. M.p. 223-224 ºC] [27]; IR (KBr) υ (cm^{-1}): 3409, 3310, (NH_2), 3060, 2972, 2870 (CH), 2190 (CN); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.95-7.16 (m, 9H, aromatic), 5.00 (bs, 2H, NH_2), 4.98 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δc: 160.33 (C-2), 150.24 (C-10b), 144.52 (C-9), 137.46 (C-10a), 135.97 (C-7), 128.71 (C-5), 127.75 (C-6a), 123.66 (C-4a), 122.18 (C-8), 121.35 (C-6), 120.35 (CN), 55.66 (C-3), 40.64 (C-4), 143.01, 131.68, 129.57, 126.73 (aromatic); Anal. Calcd for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 68.29; H, 3.56; N, 12.48 %.

2-Amino-4-(4-bromophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3b). Pale yellow needles, yield 81%; m.p. 230-231 ºC; IR (KBr) υ (cm^{-1}): 3395, 3320, (NH_2), 3060, 3020, 2962, 2861 (CH), 2196 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 9.00-7.09 (m, 9H, aromatic), 5.22 (bs, 2H, NH_2), 4.89 (s, 1H, H-4); ^{13}C NMR (125 MHz) ($CDCl_3$) δc: 159.44 (C-2), 150.57 (C-10b), 143.39 (C-9), 137.92 (C-10a), 136.31 (C-7), 128.35 (C-5), 127.07 (C-6a), 122.18 (C-4a), 121.62 (C-8), 121.17 (C-6), 119.45 (CN), 59.85 (C-3), 41.28 (C-4), 143.22, 132.14, 129.85, 124.02 (aromatic); MS *m/z* (%): 379 [M^++2] (7), 377 [$M]^+$ (7), 222 (100), 155 (43), 113 (13), 75 (59);

Anal. Calcd for $C_{19}H_{12}BrN_3O$: C, 60.34; H, 3.20; N, 11.11. Found: C, 60.26; H, 3.18; N, 11.03 %.

2-Amino-4-(4-chlorophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3c). Colourless needles, yield 78%; m.p. 262-263 ºC; IR (KBr) υ (cm^{-1}): 3464, 3343 (NH_2), 3056, 2900, 2870 (CH), 2188 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.00-6.94 (m, 8H, aromatic), 4.98 (bs, 2H, NH_2), 4.82 (s, 1H, H-4), 2.74 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δc: 159.94 (C-2), 159.46 (C-9), 142.95 (C-10b), 137.61 (C-10a), 136.20 (C-7), 129.13 (C-5), 125.96 (C-6a), 123.85 (C-8), 123.08 (C-4a), 121.08 (C-6), 119.56 (CN), 60.13 (C-3), 41.20 (C-4), 25.62 (CH_3), 142.90, 133.36, 129.40, 126.59 (aromatic); MS *m/z* (%): 349 $[M^+$+2] (5), 347 $[M]^+$ (15), 236 (100), 208 (5), 180 (2), 124 (4), 98 (2), 75 (19); Anal. Calcd for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.14; H, 4.14; N, 12.15 %.

2-Amino-4-(4-bromophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3d). Colourless needles, yield 75%; m.p. 277-278 ºC; IR (KBr) υ (cm^{-1}): 3464, 3344 (NH_2), 3079, 3059, 2950, 2870 (CH), 2188 (CN); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.21-7.10 (m, 8H, aromatic), 7.18 (bs, 2H, NH_2), 4.97 (s, 1H, H-4), 2.70 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δc: 160.32 (C-2), 159.08 (C-9), 145.13 (C-10b), 137.01 (C-10a), 136.10 (C-7), 130.77 (C-5), 129.89 (C-6a), 126.12 (C-8), 125.75 (C-4a), 121.32 (C-6), 120.10 (CN), 142.59, 132.06, 131.62, 123.50 (aromatic), 55.66 (C-3), 41.51 (C-4), 24.96 (CH_3); MS *m/z* (%): 393 $[M^+$+2] (11), 391 $[M]^+$ (11), 236 (100), 208 (6), 180 (1), 124 (5), 99 (2), 77 (6); Anal. Calcd for $C_{20}H_{14}BrN_3O$: C, 61.24; H, 3.60; N, 10.71. Found: C, 61.21; H, 3.56; N, 10.68 %.

2-[4-(Piperidin-1-yl)benzylidene]malononitrile (5). Orange crystals, yield 76%; m.p. 122-123 ºC; [Lit. M.p. 120-121 ºC] [28]; IR (KBr) υ (cm^{-1}): 3070, 3027, 2990, 2941, 2860 (CH), 2215 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.45 (s, 1H, (=CH), 7.91-6.85 (m, 4H, aromatic), 3.53-3.51 (m, 4H, $2CH_2$), 1.76-1.67 (m, 6H, $3CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δc: 157.78 (=CH), 115.98 (CN), 154.43, 134.00, 112.96 (aromatic), 72.14 (C-2), 48.03, 25.40, 24.30 (piperidine); Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.00; H, 6.42; N, 17.84 %.

Preparation of 2-[4-(piperidin-1-yl)benzylidene]malononitrile (5) from *α*-cyano-*p*-fluoro-cinnamonitriles (2c). This compound was prepared according to the literature procedure [28].

Reaction of 8-hydroxy-2-methylquinoline (1b) with *p*-chlorobenzaldehyde

Method A. A mixture of 8-hydroxy-2-methylquinoline **1b** (0.01 mmol), *p*-chlorobenzaldehyde, (0.08 mmol) and acetic anhydride (100 ml) was heated at 150 ºC for 30 h (TLC monitoring). After cooling, the solvent was removed in vacuum, and the residue was recrystallised from ethanol/benzene to give **6**. Compound **6** was heated at 100 ºC for 1 h (TLC monitoring) in pyridine/water (v/v = 4:1) (100 ml). After cooling, the solvent was removed in vacuum to provide the crude product which recrystallised from ethanol to give **7**. The physical and spectral data of compounds **6** and **7** are as follows:

***(E)* 8-Acetoxy-2-(4-chlorostyryl)quinoline (6).** Pale yellow crystals, yield 41%; m.p. 100-101 ºC; IR (KBr) υ (cm^{-1}): 3090, 3050, 3010, 2942, 2961 (CH), 1760 (CO); ^{1}H NMR (500 MHz,

$CDCl_3$) δ_H: 8.12-7.38 (m, 9H, aromatic), 7.63 (d, *J* = 17 Hz, 1H, =CH), 7.47 (d, *J* = 17 Hz, 1H, =CH), 2.60 (s, 3H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δc: 169.83 (CO), 155.45 (C-2), 147.35 (C-8), 140.87 (C-1a), 136.53 (C-4), 134.42 (=CH), 129.35 (=CH), 128.63 (C-4a), 125.88 (C-6), 125.57 (C-5), 121.78 (C-7), 120.20 (C-3), 21.06 (CH_3), 134.96, 133.47, 129.01, 128.57 (aromatic); ^{13} C NMR-DEPT spectrum at 135º CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δc: 136.53 (C-4 ↑), 134.42 (=CH ↑), 129.35 (=CH ↑), 129.01 (aromatic ↑), 128.57 (aromatic ↑), 125.88 (C-6 ↑), 125.57 (C-5 ↑), 121.78 (C-7 ↑), 120.20 (C-3 ↑), 21.06 (CH_3 ↑). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δc: 136.53 (C-4 ↑), 134.42 (=CH ↑), 129.35 (=CH ↑), 129.01 (aromatic ↑), 128.57 (aromatic ↑), 125.88 (C-6 ↑), 125.57 (C-5 ↑), 121.78 (C-7 ↑), 120.20 (C-3 ↑). In the DEPT spectrum at 45° (CH, CH_2 and CH_3 positive) revealed signals at δc: 136.53 (C-4 ↑), 134.42 (=CH ↑), 129.35 (=CH ↑), 129.01 (aromatic ↑), 128.57 (aromatic ↑), 125.88 (C-6 ↑), 125.57 (C-5 ↑), 121.78 (C-7 ↑), 120.20 (C-3 ↑), 21.06 (CH_3 ↑); MS *m/z* (%): 325 [M^++2], (0.3), 323 [M]$^+$, (1), 283 [M]$^+$ (11), 281 [M^++2] (33), 280 (100), 170 (3), 144 (4), 113 (44), 74 (54), 50 (72); Anal. Calcd for $C_{19}H_{14}ClNO_2$: C, 70.48; H, 4.36; N, 4.33. Found: C, 70.49; H, 4.39; N, 4.36 %.

***(E)* 2-(4-Chlorostyryl)-8-hydroxyquinoline (7).** Yellow needles, yield 34%; m.p. 142-143 ºC; [Lit. m.p. 150 ºC] [1f,g]; IR (KBr) υ (cm^{-1}): 3349 (OH), 3050, 3020, 2972, 2865 (CH); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 9.85 (bs, 1H, OH), 8.32-7.12 (m, 9H, aromatic), 8.14 (d, *J* = 16 Hz, 1H, =CH), 7.51 (d, *J* = 16. Hz, 1H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δc: 160.25 (C-2), 153.10 (C-8), 138.12 (C-1a), 136.54 (C-4), 135.15 (=CH), 131.62 (=CH), 129.58 (C-4a), 127.72 (C-6), 121.04 (C-3), 117.55 (C-5), 111.21 (C-7), 135.44, 133.18, 128.96, 128.91 (aromatic); MS *m/z* (%): 283 [M^++2] (32), 281 [M]$^+$ (100), 170 (2), 144 (4), 113 (31), 74 (18), 50 (31); Anal. Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.50; H, 4.31; N, 4.99 %.

Method B. 8-Hydroxy-2-methylquinoline **1b** (0.01 mmol) and *p*-chlorobenzaldehyde (0.02 mmol) were mixed thoroughly using mortar and put in an open vessel. Then the mixture was exposed to Microwave irradiation for 4 min. The oven was operated at 70% power (560W) in a two step mode with interval (2 min-30s-2 min). After the reaction, the mixture was allowed to cool down and Et_2O (10 ml) was added. The crude product was filtered, washed with Et_2O (15 ml) and purified by recrystallization from ethanol to give **7** (m.p. and mixed m.p.) yield 40%; (Lit. m.p. 150 ºC)[1f,g]

General procedure for the preparation of 9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline derivatives (8a,b and 9a,b)

A solution of *(E)* 2-(4-chlorostyryl)-8-hydroxyquinoline **7** (0.01 mmol) in EtOH (30 ml) was treated with *α*-cyano-*p*-chloro/bromocinnamonitrile **2a,b** (0.01 mmol) or ethyl *α*-cyano-*p*-chloro/bromocinnamate **2d,e** (0.01 mmol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation occurred (reaction times: 15 min. for **2a,b** and 30 min. for **2d,e**). The solid product which formed was collected by filtration and recrystallised from benzene or ethanol to give **8a,b** and **9a,b**. The physical and spectral data of compounds **8a,b** and **9a,b** are as follows:

(E) **2-Amino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (8a).** Pale yellow needles, yield 91%; m.p. 244-245 ºC; IR (KBr) υ (cm^{-1}): 3417, 3310, 3182 (NH_2), 3070, 3040, 2950, 2872 (CH), 2189 (CN); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.34-7.14 (m, 12H, aromatic), 8.00 (d, *J* = 16.5 Hz, 1H, =CH), 7.52 (d, *J* = 16.5 Hz, 1H, =CH), 7.21 (bs, 2H, NH_2 cancelled by D_2O), 5.01 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δc: 160.25 (C-2), 155.13(C-9), 144.59 (C-10b), 137.44 (C-10a), 136.53 (C-7), 133.18 (=CH), 128.95 (=CH), 128.72 (C-5), 126.89 (C-6a), 123.41 (C-8), 121.72 (C-4a), 121.00 (C-6), 120.28 (CN), 56.00 (C-3), 40.42 (C-4), 142.82, 135.15, 133.42, 131.26, 129.57, 128.89, 126.34 (aromatic); ^{13} C NMR-DEPT spectrum at 135º CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δc: 136.53 (C-7 ↑), 133.42 (aromatic ↑), 133.18 (=CH ↑), 129.57 (aromatic ↑), 128.95 (=CH ↑), 128.89 (aromatic ↑), 128.72 (C-5 ↑), 126.34, (aromatic ↑), 123.41 (C-8 ↑), 121.00 (C-6 ↑), 40.42 (C-4 ↑). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δc: 136.53 (C-7 ↑), 133.42 (aromatic ↑), 133.18 (=CH ↑), 129.57 (aromatic ↑), 128.95 (=CH ↑), 128.89 (aromatic ↑), 128.72 (C-5 ↑), 126.34, (aromatic ↑), 123.41 (C-8 ↑), 121.00 (C-6 ↑), 40.42 (C-4 ↑). In the DEPT spectrum at 45° (CH, CH_2 and CH_3 positive) revealed signals at δc: 136.53 (C-7 ↑), 133.42 (aromatic ↑), 133.18 (=CH ↑), 129.57 (aromatic ↑), 128.95 (=CH ↑), 128.89 (aromatic ↑), 128.72 (C-5 ↑), 126.34, (aromatic ↑), 123.41 (C-8 ↑), 121.00 (C-6 ↑), 40.42 (C-4 ↑); MS *m/z* (%): 473 [M^++4] (2.71), 471 [M^++2] (18.51), 469 [M]$^+$ (28.91), 360 [M^++2] (30.97), 358 [M]$^+$ (93.49), 247 (3), 221(3), 166 (29), 126 (68), 74 (100), 50 (75); Anal. Calcd for $C_{27}H_{17}Cl_2N_3O$: C, 68.95; H, 3.64; N, 8.93. Found: C, 69.01; H, 3.69; N, 8.99 %.

(E) **2-Amino-4-(4-bromophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (8b).** Pale yellow needles, yield 90%; m.p. 254-255 ºC; IR (KBr) υ (cm^{-1}): 3384, 3315, 3199 (NH_2), 3080, 3050, 2968, 2872 (CH), 2198 (CN); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.34-7.14 (m, 12H, aromatic), 8.00 (d, *J* = 16 Hz, 1H, =CH), 7.53 (d, *J* = 16 Hz, 1H, =CH), 7.21 (bs, 2H, NH_2, cancelled by D_2O), 5.00 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δc: 160.25 (C-2), 155.14 (C-9), 145.00 (C-10b), 137.43, (C-10a), 136.53 (C-7), 133.43 (=CH), 128.95 (=CH), 126.89 (C-6a), 126.33 (C-5), 121.65 (C-4a), 123.41 (C-6), 121.00 (C-8), 120.15 (CN), 56.01 (C-3), 40.50 (C-4), 142.82, 135.15, 133.19, 131.64, 129.94, 128.89, 128.29, 120.28 (aromatic); ^{13} C NMR-DEPT spectrum at 135º CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δc: 136.53 (C-7 ↑), 133.43 (=CH ↑), 131.64 (aromatic ↑), 129.94 (aromatic ↑), 128.89 (aromatic ↑), 128.29 (aromatic ↑), 128.95 (=CH ↑), 126.33 (C-5 ↑), 123.41 (C-6 ↑), 121.00 (C-8 ↑), 40.50 (C-4 ↑). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δc: 136.53 (C-7 ↑), 133.43 (=CH ↑), 131.64 (aromatic ↑), 129.94 (aromatic ↑), 128.89 (aromatic ↑), 128.29 (aromatic ↑), 128.95 (=CH ↑), 126.33 (C-5 ↑), 123.41 (C-6 ↑), 121.00 (C-8 ↑), 40.50 (C-4 ↑). In the DEPT spectrum at 45° (CH, CH_2 and CH_3 positive) revealed signals at δc: 136.53 (C-7 ↑), 133.43 (=CH ↑), 131.64 (aromatic ↑), 129.94 (aromatic ↑), 128.89 (aromatic ↑), 128.29 (aromatic ↑), 128.95 (=CH ↑), 126.33 (C-5 ↑), 123.41 (C-6 ↑), 121.00 (C-8 ↑), 40.50 (C-4 ↑); MS *m/z* (%): 517 [M^++4] (1.55), 515 [M^++2] (5.95), 513 [M]$^+$ (4.55), 360 [M^++2] (33.42), 358 [M]$^+$ (100), 221 (2), 166 (19), 101 (26), 75 (70), 50 (42); Anal. Calcd for $C_{27}H_{17}BrClN_3O$: C, 62.99; H, 3.33; N, 8.16. Found: C, 63.02; H, 3.35; N, 8.19 %.

(E) **Ethyl 2-amino-4-(4-chlorophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate (9a).** Colourless needles, from ethanol; m.p. 192-193 ºC; 82%; IR (KBr) υ (cm^{-1}): 3409, 3296 (NH_2), 3050, 3035, 2980, 2930, 2900 (CH), 1677 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.12-7.19 (m, 12H, aromatic), 7.67 (d, *J* = 16.5 Hz, 1H, =CH), 7.27 (d, *J* = 16.5 Hz, 1H, =CH), 6.88 (bs, 2H, NH_2), 5.09 (s, 1H, H-4), 4.13 (q, *J* = 7 Hz, 2H, CH_2), 1.22 (t, *J* = 7 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δc: 169.06 (CO), 160.29 (C-2), 155.69 (C-9), 145.77 (C-10b), 142.85 (C-10a), 134.78 (C-7), 134.35 (=CH), 129.30 (=CH), 128.43 (C-5), 127.29 (C-6a), 125.48 (C-4a), 123.20 (C-6), 119.53 (C-8), 77.89 (C-3), 59.59 (CH_2), 40.71 (C-4), 14.39 (CH_3), 136.98, 134.64, 133.04, 132.09, 129.09, 128.57, 127.51, 126.93 (aromatic); MS *m/z* (%): 516 $[M]^+$ (3), 444 (4), 282 $[M^+$+2], (31.67), 280 $[M]^+$, (97.74), 170 (3), 101 (46), 75(100), 50 (58); Anal. Calcd for $C_{29}H_{22}Cl_2N_2O_3$: C, 67.32; H, 4.29; N, 5.41. Found: C, 67.28; H, 4.27; N, 5.39 %.

(E) **Ethyl 2-amino-4-(4-bromophenyl)-9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylate (9b)**. Colourless needles, yield 81%; m.p. 206-207 ºC; IR (KBr) υ (cm^{-1}): 3418, 3297 (NH_2), 3050, 3046, 2985, 2930 (CH), 1674 (CO); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 9.61 (bs, 2H, NH_2, cancelled by D_2O), 8.33-7.23 (m, 12H, aromatic), 8.15 (d, *J* = 16 Hz, 1H, =CH), 7.98 (d, *J* = 16 Hz, 1H, =CH), 5.09 (s, 1H, H-4), 4.01 (q, *J* = 7 Hz, 2H, CH_2), 1.10 (t, *J* = 7 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δc: 168.14 (CO), 160.81 (C-2), 155.11 (C-9), 152.93 (C-10b), 142.77 (C-10a), 136.51 (C-7), 135.17 (=CH), 129.64 (=CH), 128.88 (C-5), 127.72 (C-6a), 121.5 (C-4a), 119.13 (C-6), 117.55 (C-8), 75.70 (C-3), 58.75 (CH_2), 40.09 (C-4), 14.27 (CH_3), 147.14, 138.12, 133.30, 132.92, 131.13, 129.12, 128.97, 124.95 (aromatic); MS *m/z* (%): 560 $[M]^+$, (4), 406 (5), 280 (82), 225 (6), 101 (32), 75 (35), 62 (100) ; Anal. Calcd for $C_{29}H_{22}BrClN_2O_3$: C, 61.99; H, 3.95; N, 4.99. Found: C, 62.02; H, 4.00; N, 5.03 %.

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