

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

Ahmed M. El-Agrody * and Abdullah M. Al-Ghamdi

Chemistry Department, Faculty of Science, King Khalid University, 9004, Abha, Saudi Arabia

E-mail: elagrody_am@yahoo.com

DOI: <http://dx.doi.org/10.3998/ark.5550190.0012.b12>

Abstract

Treatment of 8-hydroxyquinoline **1a** and 8-hydroxy-2-methylquinoline **1b** with α -cyano-*p*-chloro/bromocinnamonnitriles **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/bromocinnamonnitriles **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*-fluorocinnamonnitrile **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/bromocinnamonnitriles and ethyl α -cyano-*p*-chloro/bromocinnamates are discussed in this work. Structures of these compounds were established on the basis of IR, ¹H NMR, ¹³C NMR, ¹³C NMR-DEPT and MS data.

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

Introduction

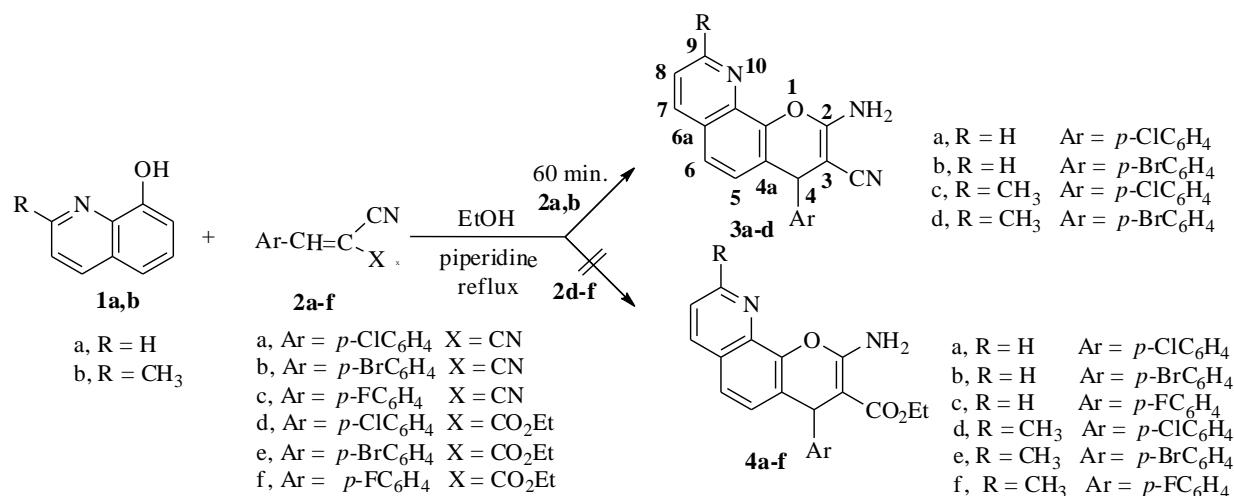
Quinoline moiety is present in many classes of biologically active compounds ¹. The biological activity of these quinoline derivatives depends not only on the bicyclic hetero-aromatic pharmacophore but also on the nature of the peripheral substituent and their spatial relationship. They also exhibit 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 inhibitors¹¹ and also, for their extensive biological activities.^{11b-d, 11c}

In continuation of the previous works¹²⁻²⁶, it seemed interesting to synthesize new 4*H*-pyrano[3,2-*h*]quinoline derivatives by using α -cyano-*p*-halocinnamonnitriles and ethyl α -cyano-*p*-halocinnamates and evaluation of their antimicrobial and antitumor activities. The observation of the reactivity of 2-hydroxyquinoline and its 2-substituted derivatives towards α -cyano-*p*-halocinnamonnitriles and ethyl α -cyano-*p*-halocinnamates are discussed in this work.

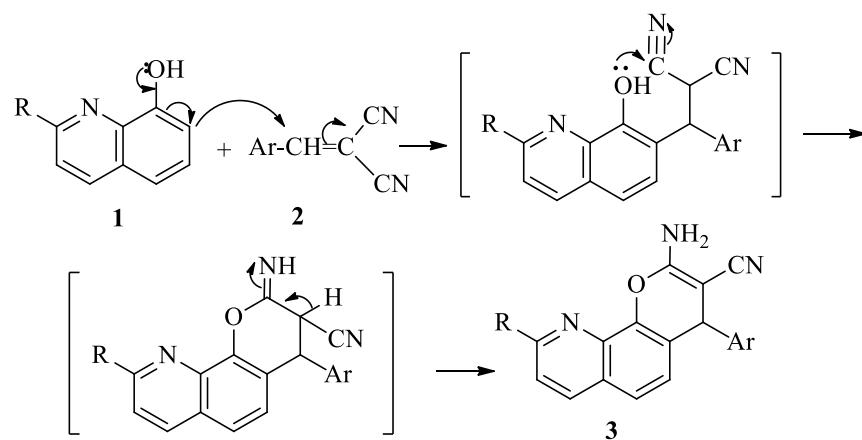
Results and Discussion

Treatment of 8-hydroxyquinoline **1a** and 8-hydroxy-2-methylquinoline **1b** with α -cyano-*p*-chloro/bromocinnamonnitrile **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 formed²⁷ (Scheme 1).

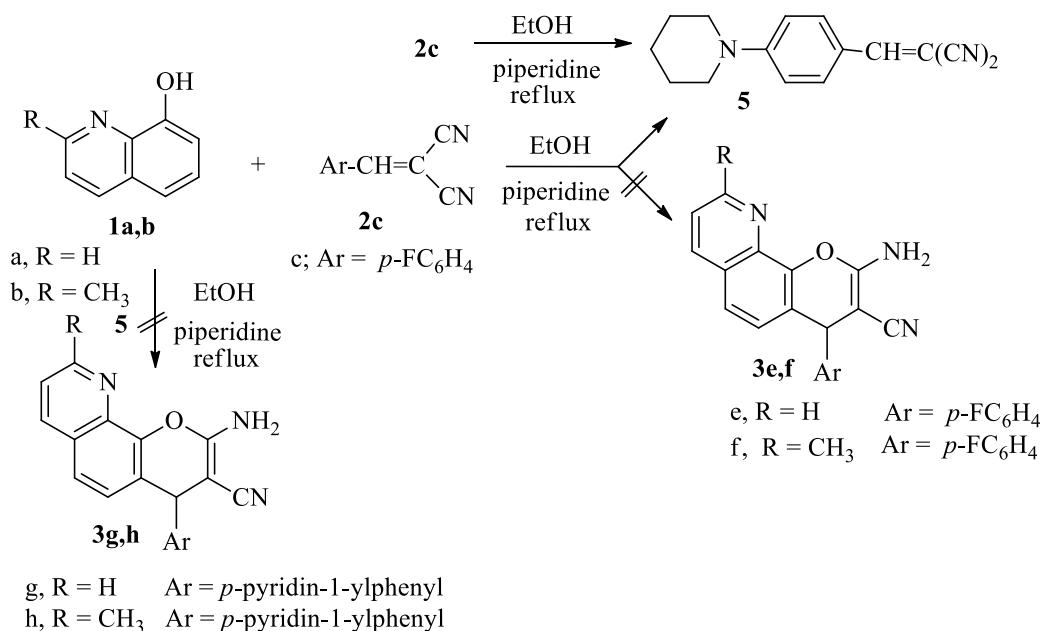


Scheme 1. Synthesis of 4*H*-pyrano[3,2-*h*]quinoline derivatives **3a-d**.

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*-fluorocinnamone **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 piperidine²⁸⁻³¹ 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 formed²⁸ (Scheme 3).

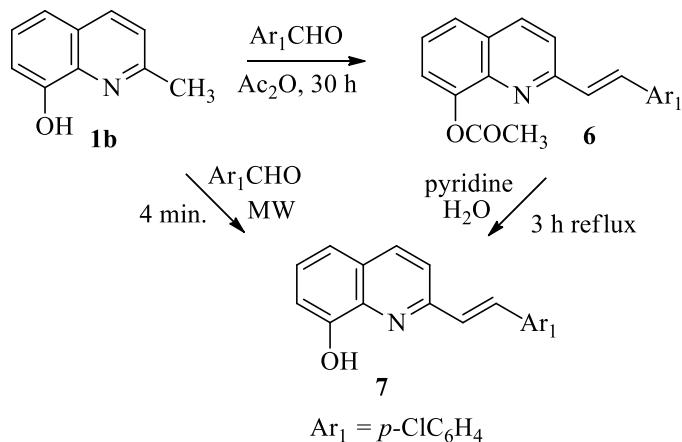
**Scheme 3.** Synthesis of 2-[4-(piperidin-1-yl)-benzylidene]malononitrile.

Structure of **5** was also supported by an independent synthesis of the same compound by nucleophilic substitution of the fluorine atom of **2c** with piperidine²⁸ 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 NH₂ stretch at ν 3464-3395, 3344-3310 cm⁻¹ and a CN stretch at ν 2196-2188 cm⁻¹. NMR spectra of **3a-d** showed characteristic signals for 4H-pyran: singlets at δ 4.98-4.82 ppm in the ¹H NMR and 41.51-40.46 ppm in the ¹³C 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**.



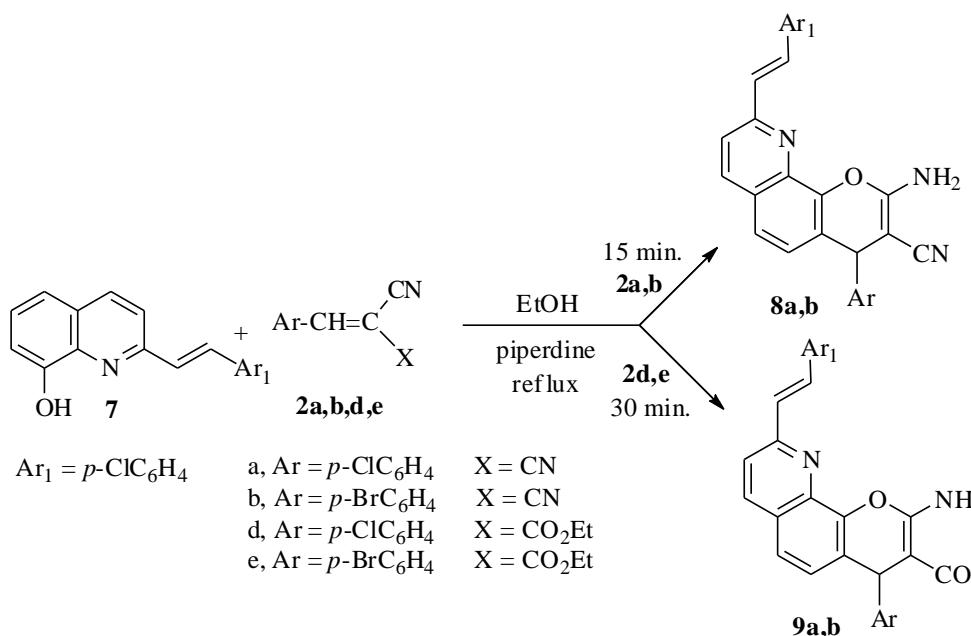
Scheme 4. Preparation of (*E*) 8-acetoxy-2-(4-chlorostyryl)quinoline **6** and (*E*) 8-hydroxy-2-(4-chlorostyryl)quinoline **7**.

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 ν 1760 cm⁻¹ while for **7** showed the appearance of a OH stretch at ν 3349 cm⁻¹. The ¹H and ¹³C 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, COCH₃) and 134.42 (=CH), 129.35 (=CH), 21.06 ppm (CH₃). The ¹³C NMR-DEPT spectrum at 45°, 90° and 135° of **6** provided additional evidence in support of the proposed structure. The ¹³C NMR-DEPT spectrum of **6** at δ 135° CH, CH₃ [positive (up)], CH₂ [negative (down)], revealed the following signals at δ 134.42 (=CH ↑), 129.35 (=CH ↑), 21.06 (CH₃ ↑), while at 90° only CH signals are positive (up) and showed at δ 134.42 (=CH ↑), 129.35 (=CH ↑) and at 45° (CH, CH₂ and CH₃ positive) revealed signals at δ 134.42 (=CH ↑), 129.35 (=CH ↑), 21.06 (CH₃ ↑). 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**.

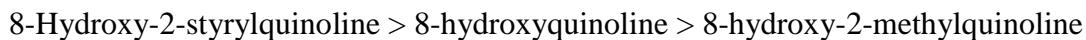
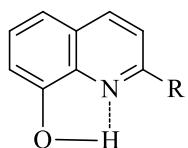


Scheme 5. Synthesis of 9-(4-chlorostyryl)-4*H*-pyrano[3,2-*h*]quinoline derivatives **8a,b** and **9a,b**.

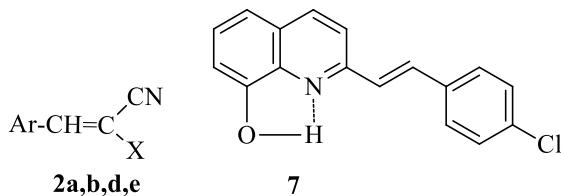
The structures **8** and **9** were established on the basis of spectral data. The IR spectra of **8a,b** showed the appearance of the a NH₂ stretch at ν 3417-3384, 3315-3310, 3199-3182 cm⁻¹ a CN stretch at ν 2198-2189 cm⁻¹ while a NH₂ stretch at ν 3409-3380, 3349-3296 cm⁻¹ and a CO stretch at ν 1677-1643 cm⁻¹ for **9a,b**. The ¹H and ¹³C 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 ¹H signals at 4.13-4.01 (q, $J = 7$ Hz, 2H, CH₂), 1.22-1.10 (t, $J = 7$ Hz, 3H, CH₃) with the corresponding signals in the ¹³C spectra at δ 59.59-58.75 (CH₂) and 14.39-14.27 ppm (CH₃) respectively. The ¹³C NMR-DEPT spectra at 45°, 90° and 135° of compounds **8a,b** provided additional evidence in support of the proposed structures. Also, the 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/bromocinnamonnitriles **2a,b** and ethyl α -cyano-*p*-chloro/bromocinnamates **2d,e** follows the following sequence:



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).



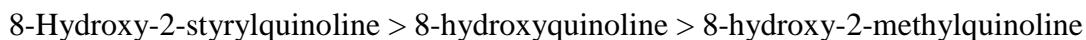
- a, Ar = *p*-ClC₆H₄ X = CN
- b, Ar = *p*-BrC₆H₄ X = CN
- d, Ar = *p*-ClC₆H₄ X = CO₂Et
- e, Ar = *p*-BrC₆H₄ X = CO₂Et

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/bromocinnamonnitriles **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/bromocinnamonnitriles 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:



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. ¹H NMR and ¹³C 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. ¹³C NMR spectra were obtained using distortionless enhancement by polarization transfer (DEPT), with this technique, the signals of CH & CH₃ carbon atoms appears normal (up) and the signal of carbon atoms in CH₂ 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/fluorocinnamonnitriles **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 °C; [Lit. M.p. 223-224 °C]²⁷; IR (KBr) ν (cm⁻¹): 3409, 3310, (NH₂), 3060, 2972, 2870 (CH), 2190 (CN); ¹H NMR (500 MHz, DMSO-*d*₆) δ_H: 8.95-7.16 (m, 9H, aromatic), 5.00 (bs, 2H, NH₂), 4.98 (s, 1H, H-4); ¹³C NMR (125 MHz, DMSO-*d*₆) δ_C: 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 C₁₉H₁₂ClN₃O: 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 °C; IR (KBr) ν (cm⁻¹): 3395, 3320, (NH₂), 3060, 3020, 2962, 2861 (CH), 2196 (CN); ¹H NMR (500 MHz, CDCl₃) δ_H: 9.00-7.09 (m, 9H, aromatic), 5.22 (bs, 2H, NH₂), 4.89 (s, 1H, H-4); ¹³C NMR (125 MHz) (CDCl₃) δ_C: 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 C₁₉H₁₂BrN₃O: 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-4H-pyrano[3,2-h]quinoline-3-carbonitrile (3c). Colourless needles, yield 78%; m.p. 262-263 °C; IR (KBr) ν (cm⁻¹): 3464, 3343 (NH₂), 3056, 2900, 2870 (CH), 2188 (CN); ¹H NMR (500 MHz, CDCl₃) δ _H: 8.00-6.94 (m, 8H, aromatic), 4.98 (bs, 2H, NH₂), 4.82 (s, 1H, H-4), 2.74 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ _C: 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 (CH₃), 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 C₂₀H₁₄ClN₃O: 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-4H-pyrano[3,2-h]quinoline-3-carbonitrile (3d). Colourless needles, yield 75%; m.p. 277-278 °C; IR (KBr) ν (cm⁻¹): 3464, 3344 (NH₂), 3079, 3059, 2950, 2870 (CH), 2188 (CN); ¹H NMR (500 MHz, DMSO-*d*₆) δ _H: 8.21-7.10 (m, 8H, aromatic), 7.18 (bs, 2H, NH₂), 4.97 (s, 1H, H-4), 2.70 (s, 3H, CH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ _C: 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 (CH₃); 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 C₂₀H₁₄BrN₃O: 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 °C; [Lit. M.p. 120-121 °C]²⁸; IR (KBr) ν (cm⁻¹): 3070, 3027, 2990, 2941, 2860 (CH), 2215 (CN); ¹H NMR (500 MHz, CDCl₃) δ _H: 7.45 (s, 1H, (=CH), 7.91-6.85 (m, 4H, aromatic), 3.53-3.51 (m, 4H, 2CH₂), 1.76-1.67 (m, 6H, 3CH₂); ¹³C NMR (125 MHz, CDCl₃) δ _C: 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 C₁₅H₁₅N₃: 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*-fluorocinnamnitriles (2c). This compound was prepared according to the literature procedure²⁸.

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 °C 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 °C 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 °C; IR (KBr) ν (cm⁻¹): 3090, 3050, 3010, 2942, 2961 (CH), 1760 (CO); ¹H 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) δ_{C} : 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 135° CH, CH_3 [positive (up)], CH_2 [negative (down)], revealed the following signals at δ_{C} : 136.53 (C-4 \uparrow), 134.42 (=CH \uparrow), 129.35 (=CH \uparrow), 129.01 (aromatic \uparrow), 128.57 (aromatic \uparrow), 125.88 (C-6 \uparrow), 125.57 (C-5 \uparrow), 121.78 (C-7 \uparrow), 120.20 (C-3 \uparrow), 21.06 (CH_3 \uparrow). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δ_{C} : 136.53 (C-4 \uparrow), 134.42 (=CH \uparrow), 129.35 (=CH \uparrow), 129.01 (aromatic \uparrow), 128.57 (aromatic \uparrow), 125.88 (C-6 \uparrow), 125.57 (C-5 \uparrow), 121.78 (C-7 \uparrow), 120.20 (C-3 \uparrow). In the DEPT spectrum at 45° (CH, CH_2 and CH_3 positive) revealed signals at δ_{C} : 136.53 (C-4 \uparrow), 134.42 (=CH \uparrow), 129.35 (=CH \uparrow), 129.01 (aromatic \uparrow), 128.57 (aromatic \uparrow), 125.88 (C-6 \uparrow), 125.57 (C-5 \uparrow), 121.78 (C-7 \uparrow), 120.20 (C-3 \uparrow), 21.06 (CH_3 \uparrow); MS m/z (%): 325 [$\text{M}^{+}+2$], (0.3), 323 [$\text{M}]^+$, (1), 283 [$\text{M}]^+$ (11), 281 [$\text{M}^{+}+2$] (33), 280 (100), 170 (3), 144 (4), 113 (44), 74 (54), 50 (72); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{ClNO}_2$: 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 °C; [Lit. m.p. 150 °C]^{1f,g}; IR (KBr) ν (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) δ_{C} : 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 [$\text{M}^{+}+2$] (32), 281 [$\text{M}]^+$ (100), 170 (2), 144 (4), 113 (31), 74 (18), 50 (31); Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{ClNO}$: 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 °C)^{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)-4H-pyrano[3,2-h]quinoline-3-carbonitrile (8a). Pale yellow needles, yield 91%; m.p. 244-245 °C; IR (KBr) ν (cm⁻¹): 3417, 3310, 3182 (NH₂), 3070, 3040, 2950, 2872 (CH), 2189 (CN); ¹H 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, NH₂ cancelled by D₂O), 5.01 (s, 1H, H-4); ¹³C NMR (125 MHz, DMSO-*d*₆) δ _C: 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); ¹³C NMR-DEPT spectrum at 135° CH, CH₃ [positive (up)], CH₂ [negative (down)], revealed the following signals at δ _C: 136.53 (C-7 \uparrow), 133.42 (aromatic \uparrow), 133.18 (=CH \uparrow), 129.57 (aromatic \uparrow), 128.95 (=CH \uparrow), 128.89 (aromatic \uparrow), 128.72 (C-5 \uparrow), 126.34, (aromatic \uparrow), 123.41 (C-8 \uparrow), 121.00 (C-6 \uparrow), 40.42 (C-4 \uparrow). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δ _C: 136.53 (C-7 \uparrow), 133.42 (aromatic \uparrow), 133.18 (=CH \uparrow), 129.57 (aromatic \uparrow), 128.95 (=CH \uparrow), 128.89 (aromatic \uparrow), 128.72 (C-5 \uparrow), 126.34, (aromatic \uparrow), 123.41 (C-8 \uparrow), 121.00 (C-6 \uparrow), 40.42 (C-4 \uparrow). In the DEPT spectrum at 45° (CH, CH₂ and CH₃ positive) revealed signals at δ _C: 136.53 (C-7 \uparrow), 133.42 (aromatic \uparrow), 133.18 (=CH \uparrow), 129.57 (aromatic \uparrow), 128.95 (=CH \uparrow), 128.89 (aromatic \uparrow), 128.72 (C-5 \uparrow), 126.34, (aromatic \uparrow), 123.41 (C-8 \uparrow), 121.00 (C-6 \uparrow), 40.42 (C-4 \uparrow); 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 C₂₇H₁₇Cl₂N₃O: 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)-4H-pyrano[3,2-h]quinoline-3-carbonitrile (8b). Pale yellow needles, yield 90%; m.p. 254-255 °C; IR (KBr) ν (cm⁻¹): 3384, 3315, 3199 (NH₂), 3080, 3050, 2968, 2872 (CH), 2198 (CN); ¹H 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, NH₂, cancelled by D₂O), 5.00 (s, 1H, H-4); ¹³C NMR (125 MHz, DMSO-*d*₆) δ _C: 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); ¹³C NMR-DEPT spectrum at 135° CH, CH₃ [positive (up)], CH₂ [negative (down)], revealed the following signals at δ _C: 136.53 (C-7 \uparrow), 133.43 (=CH \uparrow), 131.64 (aromatic \uparrow), 129.94 (aromatic \uparrow), 128.89 (aromatic \uparrow), 128.29 (aromatic \uparrow), 128.95 (=CH \uparrow), 126.33 (C-5 \uparrow), 123.41 (C-6 \uparrow), 121.00 (C-8 \uparrow), 40.50 (C-4 \uparrow). In the DEPT spectrum at 90° only CH signals are positive (up) and showed δ _C: 136.53 (C-7 \uparrow), 133.43 (=CH \uparrow), 131.64 (aromatic \uparrow), 129.94 (aromatic \uparrow), 128.89 (aromatic \uparrow), 128.29 (aromatic \uparrow), 128.95 (=CH \uparrow), 126.33 (C-5 \uparrow), 123.41 (C-6 \uparrow), 121.00 (C-8 \uparrow), 40.50 (C-4 \uparrow). In the DEPT spectrum at 45° (CH, CH₂ and CH₃ positive) revealed signals at δ _C: 136.53 (C-7 \uparrow), 133.43 (=CH \uparrow), 131.64 (aromatic \uparrow), 129.94 (aromatic \uparrow), 128.89 (aromatic \uparrow), 128.29 (aromatic \uparrow), 128.95 (=CH \uparrow), 126.33 (C-5 \uparrow), 123.41 (C-6 \uparrow), 121.00 (C-8 \uparrow), 40.50 (C-4 \uparrow); 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 C₂₇H₁₇BrCl₂N₃O: 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)-4H-pyrano[3,2-h]quinoline-3-carboxylate (9a). Colourless needles, from ethanol; m.p. 192-193 °C; 82%; IR (KBr) ν (cm⁻¹): 3409, 3296 (NH₂), 3050, 3035, 2980, 2930, 2900 (CH), 1677 (CO); ¹H NMR (500 MHz, CDCl₃) 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, NH₂), 5.09 (s, 1H, H-4), 4.13 (q, *J* = 7 Hz, 2H, CH₂), 1.22 (t, *J* = 7 Hz, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ _C: 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 (CH₂), 40.71 (C-4), 14.39 (CH₃), 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 C₂₉H₂₂Cl₂N₂O₃: 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)-4H-pyrano[3,2-h]quinoline-3-carboxylate (9b). Colourless needles, yield 81%; m.p. 206-207 °C; IR (KBr) ν (cm⁻¹): 3418, 3297 (NH₂), 3050, 3046, 2985, 2930 (CH), 1674 (CO); ¹H NMR (500 MHz, DMSO-*d*₆) δ _H: 9.61 (bs, 2H, NH₂, cancelled by D₂O), 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, CH₂), 1.10 (t, *J* = 7 Hz, 3H, CH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ _C: 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 (CH₂), 40.09 (C-4), 14.27 (CH₃), 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 C₂₉H₂₂BrClN₂O₃: C, 61.99; H, 3.95; N, 4.99. Found: C, 62.02; H, 4.00; N, 5.03 %.

Acknowledgements

This study was supported by the King Abdulaziz City for Science and Technology (KACST), No. A-S-11-0560. We also deeply thanks Mr. Ali Y. A. Alshahrani for making the ¹H NMR and ¹³C NMR samples.

References

1. (a) Ramesh, R. D.; Manian, R. S. ; Raghunathan, R.; Sainath, S.; Raghunathan, M. *Bioorg. Med. Chem.* **2009**, *17*, 660. (b) Larghi, E. L.; Bohn, M. L.; Kaufman, T. S. *Tetrahedron* **2009**, *65*, 4257. (c) Xin-Hua Liu, Jing Zhu, An-na Zhou, Bao-An Song, Hai-Liang Zhu, Lin-Shan bai, Pinaki S. Bhadury, Chun-Xiu Pan, *Bioorg. Med. Chem.* **2009**, *17*, 1207. (d) Ganesh, T.; Min, J.; Thepchatri, P.; Du, Y.; Li, L.; Lewis, I.; Wilson, L.; Chiosis, H. Fu, G.; Dingledine, R.; Liotta, D.; Snyder, J. P.; Sun, A. *Bioorg. Med. Chem.* **2008**, *16*, 6903. (e) Righi, G.; Ciambrone, S.; Bonini, C.; Campaner, P. *Bioorg. Med. Chem.* **2008**, *16*, 902. (f)

- Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Finster, J.; Kalinowski, D.; Podeszwa, B.; Niedbala, H.; Palka, A.; Polanski, J. *Bioorg. Med. Chem.* **2007**, *15*, 1280. (g)
Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. *Bioorg. Med. Chem.* **2006**, *14*, 3592. (h)
Vazquez, M. T.; Romero, M.; Pujol, M. D. *Bioorg. Med. Chem.* **2004**, *12*, 949. (i) Narendar, P.; Srinivas, U.; Ravinder, M.; Ch. Ramesh, B.; K.; Gangadasu, B.; Murthy, U. S. N.; Jayathirtha Rao, V. *Bioorg. Med. Chem.* **2006**, *14*, 4600.
2. Kaur, K.; Jain, M.; Kaur, T.; Jain, R. *Bioorg. Med. Chem.* **2009**, *17*, 3229.
3. Behforouz, M.; Cai, W.; Mohammadi, F.; Stocksdale, M. G.; Gu, Z.; Ahmadian, M.; Baty, D. E.; Etling, M. R.; Al-Anzi, C. H.; Swiftney, T. M.; Tanzer, L. R.; Merriman, R. L.; Behforouz, N. C. *Bioorg. Med. Chem.* **2007**, *15*, 495.
4. Abas, F.; Lajis, N. H.; Israf, D. A.; Khozirah, S.; Umi Kalsom, Y. *Food Chemistry* **2006**, *95*, 566.
5. Rocha, L. G.; Almeida, J. R. G. S.; Macêdo, R. O.; Barbosa-Filho, J. M. *Phytomedicine* **2005**, *12*, 514.
6. Reen-Yen Kuo, Fang-Rong Chang, Chung-Yi Chen, Che-Ming Teng, Hsin-Fu Yen, Yang-Chang Wu *Phytochemistry* **2001**, *57*, 421.
7. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nugh, R. J. *Phytochemistry* **2001**, *56*, 265.
8. Atwell, G. J.; Baguley, B.C.; Denny, W.A. *J. Med. Chem.* **1989**, *32*, 396.
9. Chen, Y. L.; Chen, I. L.; Tzeng, C. C.; Wang, T. C. *Helv. Chim. Acta* **2000**, *83*, 989.
10. Majerz-Maniecka, K.; Oleksyn, B.; Musiol, R.; Podeszwa, B.; Polanski, J. *Sci. Pharm.* **2005**, *73*, 194.
11. (a) Thomas Leonard, J.; Roy, K. *Eur. J. Med. Chem.* **2008**, *43*, 81. (b) Polanski, J.; Zouhiri, F.; Jeanson, L.; Desmaele, D.; d'Angelo, J.; Mouscadet, J.; Gieleciak, R.; Gasteiger, J.; Bret, M. L.; *J. Med. Chem.* **2002**, *45*, 4647. (c) Mekouar, K.; Mouscadet, J. F.; Desmaele, D.; Subra, F.; Leh, H.; Savoure, D.; Auclair, C.; d'Angelo, J. *J. Med. Chem.* **1998**, *41*, 2846. (d) Zouhiri, F.; Danet, M.; Bernard, C.; Normand-Bayle, M.; Mouscadet, J. F.; Leh, H.; Thomas, C. M.; Mbemba, G.; d'Angelo, J.; Desmaele, D. *Tetrahedron Lett.* **2005**, *46*, 2201. (e) Pommier, Y.; Johnson, A. A.; Marchand, C. *Nat. Rev. Drug. Discov.* **2005**, *4*, 236. (f) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721.
12. El-Agrody, A. M. *J. Chem. Res. (S)* **1994**, 280.
13. El-Agrody, A. M.; Emam, H. A.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A.H. *J. Chem. Res. (S)* **1997**, 320.
14. El-Agrody, A. M.; Emam, H. A.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A.H. *J. Chem. Res. (M)* **1997**, 2039.
15. Bedair, A. H.; El-Hady, N. A.; Abd El-Latif, M. S.; Fakery, A.H.; El-Agrody, A.M. *IL Farmaco* **2000**, *55*, 708.

16. El-Agrody, A. M.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A. H.; El-Sayed, E. S. M.; El-Ghareab, K. A. *Acta Pharm.* **2000**, *50*, 111.
17. Sayed, A. Z.; El-Hady, N. A.; El-Agrody, A. M. *J. Chem. Res. (S)* **2000**, 146.
18. El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. H.; Bedair, A. H. *Molecules* **2000**, *6*, 519.
19. Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K.A.R.; El-Agrody, A. M. *IL Farmaco* **2001**, *56*, 965.
20. El-Agrody, A. M.; Eid, F. A.; Emam, H. A.; Mohamed, H. M.; Bedair, A. H. Z. *Naturforsch., Teil B* **2002**, *57*, 579.
21. Khafagy, M. M.; Abd El-Wahab, A. H. F.; Eid, F. A.; El-Agrody, A. M. *IL Farmaco* **2002**, *57*, 715.
22. Eid, F. A.; Bedair, A. H.; Emam, H. A.; Mohamed, H. M.; El-Agrody, A. M. *Al-Azhar Bull. Sci.* **2003**, *14*, 311.
23. Abd-El-Aziz, A. S.; El-Agrody, A. M.; Bedair, A. H.; Christopher Corkery, T.; Ata, A. *Heterocycles* **2004**, *63*, 1793.
24. Abd-El-Aziz, A. S.; Mohamed, H. M.; Mohammed, S.; Zahid, S.; Ata, A.; Bedair, A. H.; El-Agrody, A. M.; Harvey, P. D. *J. Heterocycl. Chem.* **2007**, *44*, 1287.
25. Sabry, N. M.; Mohamed, H. M.; Khattab , Essam Shawky A. E. H.; Motlaq, S. S.; El-Agrody, A. M. *Eur. J. Med. Chem.* **2011**, *46*, 765.
26. El-Agrody, A. M.; Sabry, N. M.; Motlaq, S. S. *J. Chem. Res.* **2011**, *35*, 77.
27. Khalil, Z. H.; Abdel-Hafez, A. A.; Geies A. A.; kamal El-Dean, A. M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 668.
28. Bloxham, J.; Dell, C.P.; Smith, C.W. *Heterocycles* **1994**, *38*, 399.
29. El-Gaby, M. S. A. *J. of the Chinese Chem. Soc.* **2004**, *51*, 125.
30. Hendrickx, E.; Zhang, Y.; Ferrio, K. B.; Herlocker, J. A.; Anderson, J.; Armstrong, N. R.; Mash, E. A.; Persoons, A. P.; Peyghambarian, N.; Kippelen, B. *J. Mater.Chem.* **1999**, *9*, 2251.
31. Meciarova, M.; Toma, S.; Magdolen,P. *Ultrasonics Sonochemistry* **2003**, *10*, 265.