Synthesis and antimicrobial activities of pyrano[3,2-*c*]quinoline, pyrimido[5',4':5,6]pyrano[3,2-*c*]quinoline and [1,2,4]triazolo[2",3":1',6']pyrimido[5',4':5,6]pyrano[3,2-*c*]quinoline derivatives

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The synthesis of novel 7-(4-chlorophenyl)-6-hydroxy-3-methoxy-10-methyl-8, 9-dihydro-7*H*-pyrimido[5', 4':5, 6]pyrano-[3, 2-*c*]quinoline and [1, 2, 4]triazolo[2", 3":1', 6']pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline derivatives has been reported. The key intermediate 2-amino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4H-pyrano[3, 2-*c*]-quinoline-3-carbonitrile was obtained by treating 4-hydroxy-7-methoxyquinolin-2(1*H*)-one with various substituted α-cyanocinnamonitrile in ethanolic piperidine solution. Antimicrobial activity was shown for most of the synthesised compounds.

Keywords: α-cyano-p-chlorocinnamonitrile, ethyl α-cyano-p-chlorocinnamate, 4-hydroxy-7-methoxyquinolin-2(1 H)-one, pyrano [3, 2-*c*]quinoline, pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline, [1, 2, 4]triazolo[2", 3":1', 6']pyrimido[5', 4':5, 6]pyrano[3, 2-*c*] quinoline

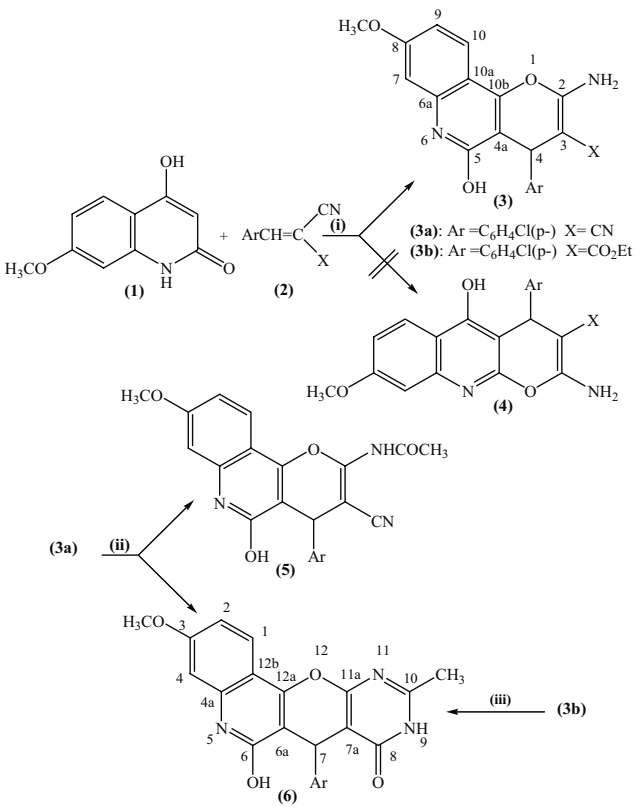
Many fused quinolines have exhibited antimicrobial activities,[1-4] antimalarial activity,[5] antitumor activity,[6] antioxidant,[7] antileishmanial[8] and antiplatelet activity.[9] Encouraged by these findings and as a continuation of our work in this area,[10] I now report the synthesis of some new 4H-pyrano[3, 2-*c*]quinolines and related derivatives. The condensation of 4-hydroxy-7-methoxyquinolin-2(1*H*)-one (**1**)[11] with various substituted α-cyanocinnamonitrile (**2a,b**) in ethanolic piperidine afforded 1:1 adducts[12,13] (Scheme 1). On the basis of ^{1}H NMR data, structure **4** was excluded. Structure **3** was established on the basis of ^{1}H NMR spectra each of which revealed a one-proton singlet at δ 4.47–4.79 ppm corresponding to the 4H-pyran in 4H-pyrano[3, 2-*c*] quinoline derivatives (**3a,b**), in addition of a –OH group at δ 11.63–11.67 ppm characteristic for structure **3** instead of a –OH group at δ 9.80–9.82 ppm for structure **4**.

The interaction of 2-amino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4*H*-pyrano[3, 2-*c*]- quinoline-3-carbonitrile (**3a**) with acetic anhydride upon reflux for 30 min, afforded the 2-acetylamino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4*H*-pyrano[3, 2-*c*]quinoline-3-carbonitrile (**5**), while heating of (**3a**) with acetic anhydride upon reflux for 6 h afforded the 7-(4-chlorophenyl)-6-hydroxy-3-methoxy-10-methyl-8, 9-dihydro-7*H*-pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinolin-8-one (**6**). The structure of (**6**) was confirmed by an independent synthesis of the same product from (**3b**) and acetonitrile in presence of gaseous HCl [14] at room temperature (Scheme 1). The structure of (**5**) and (**6**) were established by spectral data, IR, MS, ^{1}H NMR and ^{13}C NMR.

Treatment of compound **3a** with triethyl orthoformate in acetic anhydride upon reflux gave the corresponding 7-(4-chlorophenyl)-6-hydroxy-3-methoxy-10-methyl-8, 9-dihydro-7*H*-pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinolin-8-one (**6**) (m.p. and mixed m.p.), while with triethyl orthoformate without acetic anhydride afforded 4-(4-chlorophenyl)-2-ethoxymethyleneamino-5-hydroxy-8-methoxy-4H-pyrano [3, 2-*c*]quinoline-3-carbonitrile (**7**). The structure of compound (**7**) was established by its IR, MS and ^{1}H NMR.

Ammonolysis of compound (**7**) in methanol at room temperature afforded 8-amino-7-(4-chlorophenyl)-6-hydroxy-3-methoxy-7*H*-pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline (**8**), the structure of which was further supported by its independent synthesis from (**3a**) and formamide (m.p. and mixed m.p.)[12,13] (Scheme 2).

The hydrazinoloysis of compound (**7**) in ethanol at room temperature afforded 9-amino-7-(4-chlorophenyl)-6-hydroxy-3-methoxy-8-imino-8, 9-dihydro-7H-pyrimido[5', 4' : 5,-6] pyrano[3, 2-*c*]quinoline (**9a**), while the reaction of (**7**) with methylamine yielded 7-(4-chlorophenyl)-6-hydroxy-3-methoxy-8-imino-9-methyl-8, 9-dihydro-7*H*-pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline (**9b**) (Scheme 2)**.** The structure of compounds (**8, 9**) were established by spectral data, IR, MS and ^{1}H NMR.



Scheme 1 Reagents and conditions: (i) ethanol, piperidine, reflux 0.5–1 h; (ii) Ac_2O, reflux 0.5 h (for **5**); 6 h (for **6**); (iii) HCl gas/MeCN, r.t, 4–6 h.

The interaction of compound (**9a**) with triethyl orthoformate afforded 14-(4-chlorophenyl)-13-hydroxy-10-methoxy-14*H*-[1, 2, 4]triazolo[2", 3":1', 6']pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline (**10a**), while with acetyl chloride and benzoyl chloride upon reflux gave the corresponding 14-(4-chlorophenyl)-13-hydroxy-10-methoxy-2-methyl-14*H*-[1,2,4]triazolo [2", 3":1', 6']pyrimido[5', 4':5, 6]pyrano[3, 2-*c*]quinoline (**10b**) and 14-(4-chlorophenyl)-13-hydroxy-10-methoxy-2-

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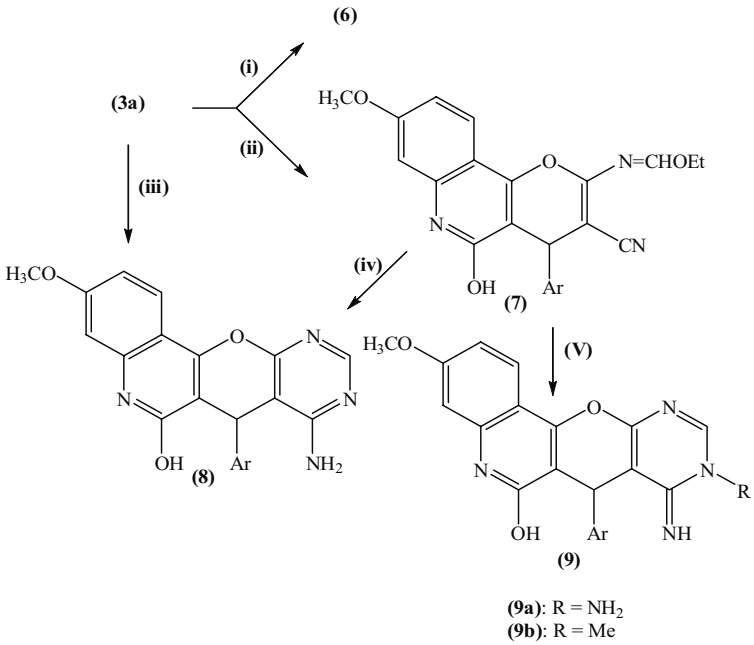


Scheme 2 Reagents and conditions: (i) $CH(OEt)_3$, Ac_2O, reflux 5 h; (ii) $CH(OEt)_3$, reflux 5 h; (iii) $HCONH_2$, reflux 6 h; (iv) NH_3 gas methanol, stirring 1 h; (v) NH_2-NH_2.H_2O(for **9a**) or $MeNH_2$(for **9b**), absolute ethanol, stirring, r.t, 1 h.

phenyl-14H-[1, 2, 4]triazolo[2", 3" : 1', 6']pyrimido[5', 4' : 5, 6] pyrano[3, 2-*c*]quinoline (**10c**) respectively (Scheme 3). The structures of (**10a–c**) were established by spectral data, IR, MS and ^{1}H NMR. Condensation of (**9a**) with benzaldehyde in ethanolic piperidine solution gave the open-chain product (**11**), which was supported by its IR, MS and ^{1}H NMR, while with benzaldehyde in dioxane piperidine gave the compound (**10c**). The structure of (**10c**) was further supported by heating compound (**11**) in dioxane piperidine[15] (m.p. and mixed m.p.) (Scheme 3).

Treatment of compound **3a** with ethanolic potassium hydroxide upon reflux afforded 4-(4-chlorophenyl)-5-hydroxy-8-methoxy-3, 4-dihydro-2H-pyrano[3, 2-*c*]quinoline-2-one (**12**) (Scheme 4), which was supported by its IR, MS and ^{1}H NMR.

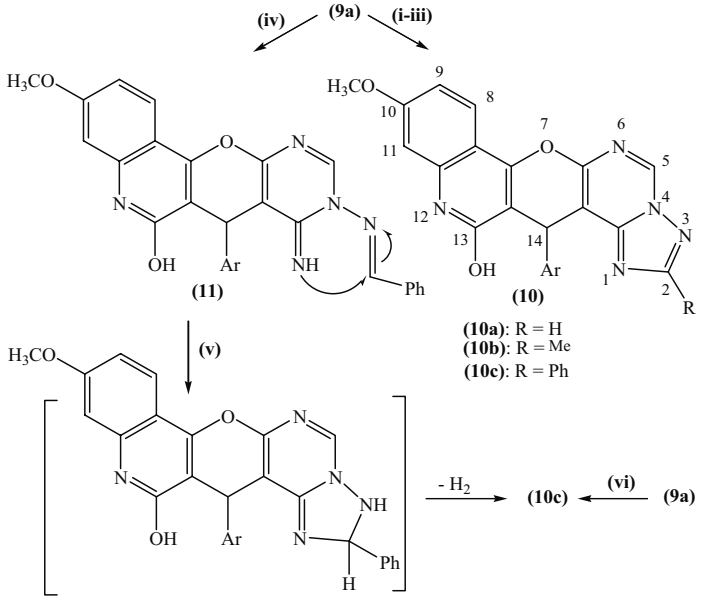
Antimicrobial activities

Applying the agar plate diffusion technique[16] the newly synthesised compounds were screened *in vitro* for antimicrobial activity against Gram positive bacteria *(Staphylococcus aureus, Bacillus subtilis),* Gram negative bacteria *(Escherichia coli, Pseudomonas aeruginosa)*, yeast *(Candida albicans)* and fungi *(Aspergillus niger)*. In this method, a standard 5 mm sterilised filter paper disc impregnated with the compound (0.3 mg/0.1 mL of dimethyl formamide) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37 °C for bacteria and 28 °C for fungi. The inhibition zone of bacterial and fungi growth around the disc was determined. The screening results are given in (Table 1). Six compounds showed moderate inhibition effect against only one of the examined Gram negative bacteria *Escherichia coli* (compound **7**, **9b** and **11**) or *Pseudomonas aeruginosa* (compound **3a**, **3b** and **9a**). Whereas seven compounds showed weak or moderate inhibition effect against only one of the examined Gram positive bacteria *Staphylococcus aureus* (compound **8**, **9a**, **10b** and **12**) or *Bacillus subtilis* (compound **7**, **10a** and **10b**). On the other hand all compounds showed high or very high antimicrobial activity against the examined pathogenic yeast *Candida albicans* except compound **6** showed moderate activity and compound **12** did not show any antimicrobial activity. Only two compounds showed weak (compound **9b**) or moderate (compound **6**) antimicrobial activity against the examined fungi *Aspergillus niger*.

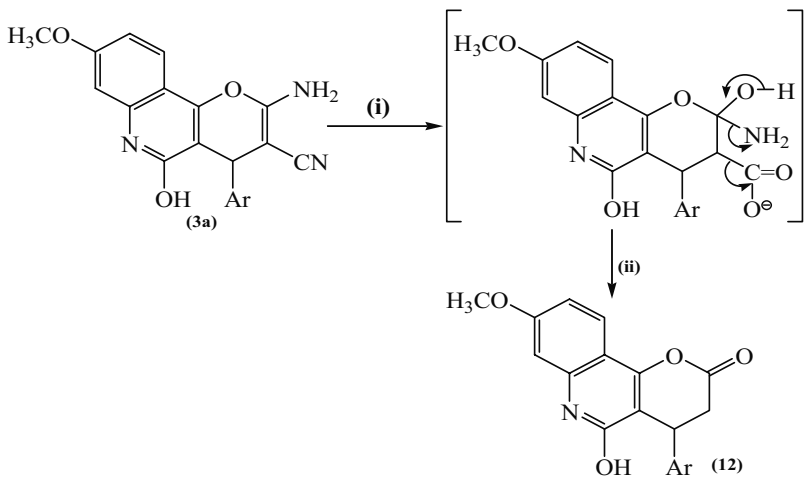
Table 1 Antibacterial and antifungal activity

Sample no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
3a	–	–	–	+ +	+ + +	–
3b	–	–	–	+ +	+ + + +	–
6	–	–	–	–	+ +	+ +
7	–	+	+ +	–	+ + + +	–
8	+ +	–	–	–	+ + +	–
9a	+	–	–	+ +	+ + + +	–
9b	–	–	+ +	–	+ + + +	+
10a	–	+ +	–	–	+ + +	–
10b	+	+	–	–	+ + + +	–
10c	–	–	–	–	+ + +	–
11	–	–	+ +	–	+ + +	–
12	+	–	–	–	–	–
Ciprofloxacin	+ + + +	+ + + +	+ + + +	+ + + +	–	–
Fungicide Nystin	–	–	–	–	+ + + +	+ + + +

Zone of inhibition: + = < 15 mm; + + = 15 – 24 mm; + + + = 25 – 34 mm; + + + + = 35 – 44 mm; – = no inhibition.



Scheme 3 Reagents and conditions: (i) $CH(OEt)_3$, dry benzene, reflux 6 h (for **10a**); (ii) AcCl, dry benzene, reflux 6 h (for **10b**); (iii) PhCOCl, dry benzene, reflux 6 h (for **10c**); (iv) PhCHO/ethanol/piperidine, reflux 2 h; (v) dioxane/piperidine/reflux 2 h; (vi) PhCHO/dioxane/piperidine/reflux 16 h.



Scheme 4 Reagents and conditions: (i) ethyl alcohol and potassium hydroxide reflux 30 min; (ii) dil. HCl.

Conclusion

It could be concluded from these results that the biologically active synthesised compounds are nearly as active as fungicide Nystin against the examined pathogenic yeast (*Candida albicans*).

Experimental

Melting points were determined in open glass capillaries and are uncorrected. The IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1430 using potassium bromide pellets and the frequencies are reported in cm^{-1}. The mass spectra were recorded on a mass spectrometer HP model MS 5988 El 70ev. The ^1H NMR and ^{13}C NMR spectra were observed on a Perkin-Elmer R12B spectrometer, and chemical shifts (δ) are in ppm relative to internal TMS. Elemental analyses were carried out in the microanalytical laboratory of the Faculty of Science, Cairo University. Reactions were routinely followed by thin layer chromatography (TLC) on silica gel; F_{254} aluminum sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

2-Amino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4H-pyrano-[3,2-c]quinoline-3-carbonitrile (**3a**)**:** A solution of 4-hydroxy-7-methoxyquinolin-2(1*H*)-one (**1**) (0.191 g, 0.001 mol) in ethanol (30 mL), piperidine (0.5 mL) and α-cyano-4-chloro- cinnamonitrile (**2a**) (0.189 g, 0.001 mol) was heated for 30 min. The solid product which formed was then collected by filtration and recrystallised from benzene to give (**3a**) (0.35 g, 79% yield) as a colourless solid, m.p. 294–295 °C; IR (cm^{-1}): 3452 (OH), 3319, 3264 (NH_2), 3058, 2922, 2818 (CH stretching), 2198 (CN) cm^{-1}; MS (*m/z*%) 379 (M^+, 12), 381 (M^+ + 2, 7.74), 278 (19), 251 (3), 225 (10), 197 (11), 169 (11), 149(25), 132 (20), 111(14), 105(22), 55 (100); ^1H NMR (DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 4.47 (s, 4-H, 1H), 6.83 (s, 2H, NH_2), 6.92–7.82 (m, 7H, ArH), 11.67 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 36.10 (C-4), 55.47(OCH_3), 98.11 (C-4a), 105.71 (C-7), 106.22 (C-10a), 111.72 (C-9), 119.71 (CN), 123.36 (C-10), 128.26, 129.29, 131.15, 139.70 (aromatic-H), 143.57 (C-8), 151.46 (C-6a), 158.91 (C-10b), 160.81 (C-5), 161.70 (C-2); Anal. Calcd for $C_{20}H_{14}ClN_3O_3$; C, 63.25; H, 3.72; N, 11.06. Found: C, 63.50; H, 3.60; N, 11.30%.

Ethyl 2-amino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4H-pyrano [3,2-c]quinoline-3-carboxylate (**3b**)**:** A solution of 4-hydroxy-7-methoxyquinolin-2(1*H*)-one (**1**) (0.191 g, 0.001 mol) in ethanol (30 mL), piperidine (0.5 mL) and ethyl α-cyano-4-chloro- cinnamate (**2b**) (0.236 g, 0.001 mol) was heated for 1 h. The solid product, which was formed, was then collected by filtration and recrystallised from ethanol to give (**3b**) (0.32 g, 74% yield) as a colourless solid, m.p. 238–239 °C; IR (cm^{-1}): 3401 (OH), 3293, 3201 (NH_2), 3073, 2973, 2911 (CH stretching), 1687 (CO ester) cm^{-1}; MS (*m/z*%) 426 (M^+, 13.24), 428 (M^+ + 2, 4.69), 335 (8.74), 337 (2.3), 315 (100), 298 (2), 278 (11), 269 (57), 242 (2), 213 (3), 151(2), 125(3), 111(2), 86(2),

63(4); ^{1}H NMR (DMSO-d_6) δ: 1.12 (t, 3H, $CH_2\underline{CH_3}$, J = 3.1 Hz), 3.82 (s, 3H, OCH_3), 4.01 (q, 2H, $\underline{CH_2}CH_3$, J = 3.1 Hz), 4.80 (s, 4-H, 1H), 6.85 (s, 2H, NH_2), 7.26-8.39 (m, 7H, ArH), 11.62 (s, 1H, OH); ^{13}C NMR (DMSO – d_6) δ 14.27(CH_3), 34.10(C-4), 55.43(OCH_3), 58.89(CH_2), 77.02(C-3), 98.14(C-4a), 105.98(C-7), 109.23(C-10a), 110.94(C-9), 123.34(C-10), 127.72, 129.71, 130.43, 139.57(aromatic-H), 145.23(C-8), 151.36(C-6a), 159.61(C-2), 161.16(C-10b), 161.53(C-5), 167.80(CO); Anal. Calcd for$C_{22}H_{19}ClN_2O_5$; C, 61.90; H, 4.49; N, 6.56. Found: C, 61.60; H, 4.60; N, 6.40%.

2-Acetylamino-4-(4-chlorophenyl)-5-hydroxy-8-methoxy-4H-pyrano[3,2-c]quinoline-3-carbonitrile (**5**): A solution of compound (**3a**) (0.38 g, 0.001 mol) in acetic anhydride (20 mL) was heated under reflux for 30 min, to give the N-acetyl derivative (**5**) (0.30 g, 79% yield) and recrystallised from ethanol to give a colourless solid, m.p. 250–251 °C; IR (cm^{-1}): 3405(OH), 3255 (NH), 2919, 2848 (CH stretching), 2204 (CN), 1675 (CO) cm^{-1}; MS (*m/z*%) 421 (M^+· 6.59), 423 (M^+ + 2, 2.53), 312 (100), 314 (42), 273 (45), 250 (1), 190.5 (18), 156 (5), 108 (69), 77 (16); ^{1}H NMR (DMSO- d_6) δ: 2.51 (s, 3H, $COCH_3$), 3.84 (s, 3H, OCH_3), 5.90 (s, 4-H, 1H), 6.64–8.32 (m, 7H, ArH), 11.52 (s, 1H, NH), 11.95 (s, 1H, OH); Anal. Calcd for $C_{22}H_{16}ClN_3O_4$, C, 62.64; H, 3.82; N, 9.96. Found: C, 62.90; H, 3.70; N, 10.20%.

7-(4-Chlorophenyl)-6-hydroxy-3-methoxy-10-methyl-8,9-dihydro-7H-pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**6**): (**a**) A solution of compound (**3a**) (0.38 g, 0.001 mol) in acetic anhydride (20 mL) was heated under reflux for 6 h to give (**6**) (0.29 g, 76% yield), which recrystallised from benzene to give a colourless solid, m.p.312–314 °C; IR (cm^{-1}): 3558 (OH), 3072 (NH), 2935, 2853 (CH stretching), 1681 (CO), 1618 (C=N) cm^{-1}; MS (*m/z*%) 421 (M^+, 1), 423(M^+ + 2, 0.1), 355 (99) 357 (36), 327 (100), 329 (35), 313 (9), 315 (3), 173 (5), 111 (5), 89(5), 63 (11); ^{1}H NMR (DMSO-d_6) δ: 1.92 (s, 3-H, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.5 (s, 7-H, 1H), 6.89–7.76 (m, 7H, ArH), 11.87 (s, 1H, OH), 11.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.06 (CH_3), 36.13 (C-7), 55.50 (OCH_3), 98.23 (C-6a), 106.09 (C-7a), 108.12 (C-4), 111.25 (C-12b), 121.14 (C-2), 123.29 (C-1), 128.57 (C-3), 128.84, 131.77, 140, 195 (aromatic-H), 143.84 (C-4a), 154.88 (C-12a), 161.24 (C-11a), 161.81 (C-10), 166.16 CO), 172.04 (C-6) Anal. Calcd for $C_{22}H_{16}ClN_3O_4$; C, 62.64; H, 3.82; N, 9.96. Found: C, 62.40; H, 3.70; N, 9.70%.

(**b**) A stream of dry gaseous HCl was passed through a mixture of (**3b**) (0.427 g, 0.001 mol) and acetonitrile (30 mL) for 6 h at room temperature. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution to give compound (**6**) (0.28 g, 65% yield).

4-(4-Chlorophenyl)-2-ethoxymethyleneamino-5-hydroxy-8-methoxy-4H-pyrano[3,2-c]quinoline-3-carbonitrile (**7**): A mixture of compound (**3a**) (0.38 g, 0.001 mol), triethyl orthoformate (0.001 mol) and acetic anhydride (20 mL) was refluxed for 5 h to give (**6**) (0.27 g, 74% yield, m.p. and mixed m.p.), while repeating the reaction without acetic anhydride for 5 h give (**7**) (0.27 g, 71% yield) which recrystallised from benzene to give a colourless solid, m.p.240–241 °C; IR (cm^{-1}): 3555(OH), 3070, 2927, 2852(CH stretching), 2052 (CN), 1620 (C=N) cm^{-1}; MS (*m/z*%) 435 (M^+, 0.3), 437 (M^+ + 2, 0.1), 363 (0.3), 337 (0.3), 226 (1), 111 (6), 72 (19), 60 (100); ^{1}H NMR (DMSO-d_6) δ: 1.34 (t, 3H, $CH_2\underline{CH_3}$, J = 1.2 Hz), 4.37 (q, 2H, $\underline{CH_2}CH_3$, J = 1.2 Hz), 3.84 (s, 3H, OCH_3), 4.5 (s, 4-H, 1H), 6.89–8.16 (m, 7H, ArH), 8.87 (s, 1H, CH=N), 11.70 (s, 1H, OH); Anal. Calcd for $C_{23}H_{18}ClN_3O_4$; C, 63.38; H, 4.16; N, 9.64. Found: C, 63.60; H, 4.30; N, 9.90%.

8-Amino-7-(4-chlorophenyl)-6-hydroxy-3-methoxy-7H-pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**8**): (**a**) A solution of compound (**3a**) (0.38 g, 0.001 mol) in formamide (20 mL) was heated under reflux for 6 h to give (**8**) (0.28 g, 74% yield), which recrystallised from benzene to give a colourless solid, m.p.216–217 °C; IR (cm^{-1}): 3482 (OH), 3394, 3153(NH_2), 1627 (C=N) cm^{-1}; MS (*m/z*%) 406 (M^+, 9.42), 408 (M^+ + 2, 3.45), 391 (3), 339 (4), 315 (100), 311 (6), 295.5 (19), 279 (52); ^{1}H NMR (DMSO-d_6) δ 3.35 (s, 3H, OCH_3), 3.78 (s, 7-H, 1H) 6.23 (s, 2H, NH_2), 6.69–7.87 (m, 7H, ArH), 8.40 (s, 10-H, 1H), 10.79 (s, 1H, OH); Anal. Calcd for $C_{21}H_{15}ClN_4O_3$; C, 62.00; H, 3.72; N, 13.77. Found: C, 61.70; H, 3.80; N, 13.50%.

(**b**) A solution of compound (**7**) (0.436 g, 0.001 mol) and gaseous NH_3 in methanol (50 mL) was stirred for 1 h at room temperature to give (**7**) (0.34 g, 89% yield).

9-Amino-7-(4-chlorophenyl)-6-hydroxy-3-methoxy-8-imino-8,9-dihydro-7H- pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**9a**)**:** A solution of compound (**7**) (0.436 g, 0.001 mol) and hydrazine hydrate (99%, 5 mL) in absolute ethanol (50 mL) was stirred at room temperature for 1 h to give (**9a**) (0.40 g, 85% yield) which recrystallised from benzene to give a colourless solid, m.p.270–271 °C; IR (cm^{-1}): 3339 (OH), 3273, 3215 (NH_2), 3192 (NH), 2921, 2628, 2134 (CH stretching), 1624 (C=N) cm^{-1}; MS (*m/z*%) 421 (M^+, 1), 423 (M^+ + 2, 0.3), 327 (100), 310 (22), 294 (64), 248 (4), 173 (6), 164 (3), 111 (7), 94 (4), 84 (5); ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 4.94 (s, 7-H, 1H), 4.99 (br, 1H, NH), 6.62 (s, 2H, NH_2), 7.15–7.82 (m, 8H, ArH), 10.73 (s, 1H, OH); Anal. Calcd for $C_{21}H_{16}ClN_5O_3$; C, 59.79; H, 3.82; N, 16.60. Found: C, 59.50; H, 3.70; N, 16.30%.

7-(4-Chlorophenyl)-6-hydroxy-3-methoxy-8-imino-9-methyl-8,9-dihydro-7H- pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**9b**)**:** Prepared from substance (**7**) (0.436 g, 0.001 mol) and methyl amine (0.001 mol) according to the procedure described above. The compound (**9b**) (0.38 g, 81% yield), which recrystallised from benzene to give a colourless solid, m.p.289–290 °C; IR (cm^{-1}): 3257 (OH), 3076 (NH), 2965, 2155 (CH stretching), 1629 (C=N)) cm^{-1}; MS (*m/z*%) 420 (M^+, 0.82), 422 (M^+ + 2, 0.55) 309 (4), 311 (1), 292 (3), 247 (2), 173 (2), 111 (24), 83 (38), 60 (100), 56 (52); ^{1}H NMR (DMSO-d_6) δ 3.01 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.89 (s, 7-H, 1H), 5.50 (s, br, 1H, NH), 6.51–8.04(m, 8H, ArH), 10.31(s, 1H, OH); Anal. Calcd for $C_{22}H_{17}ClN_4O_3$; C, 62.78; H, 4.07; N, 13.31. Found: C, 62.50; H, 3.90; N, 13.00%.

14-(4-Chlorophenyl)-13-hydroxy-10-methoxy-14H-[1,2,4]triazolo[2",3": 1',6']pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**10a**): A solution of compound (**9a**) (0.422 g, 0.001 mol) and triethyl orthoformate (0.001 mol) in dry benzene (20 mL) was refluxed for 6 h to give (**10a**) (0.46 g, 81% yield), which was recrystallised from dioxane to give a colourless solid, m.p.318–319 °C; IR (cm^{-1}): 3548 (OH), 3064, 2919, 2850 (CH stretching), 1654 (C=N) cm^{-1}; MS (*m/z*%) 431 (M^+, 1), 433 (M^+ + 2, 0.56), 417 (1), 320 (1), 258 (0.5), 173 (0.5), 111 (24), 94 (13), 67 (14), 57 (100), 55 (59); ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 4.50 (s, 14-H, 1H), 6.89-7.76 (m, 9H, ArH, 2-H, 5-H), 11.86 (s, 1H, OH); Anal. Calcd for $C_{22}H_{14}ClN_5O_3$; C, 61.19; H, 3.27; N, 16.22. Found: C, 60.90; H, 3.40; N, 16.50%.

14-(4-Chlorophenyl)-13-hydroxy-10-methoxy-2-methyl-14H-[1,2,4]triazolo[2",3": 1',6']pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**10b**): Prepared from (**9a**) (0.422 g, 0.001 mol) and acetyl chloride (0.001 mol) according to the procedure described above to give (**10b**) (0.43 g, 86% yield), which recrystallised from dioxane to give a colourless solid, m.p.280–281 °C; IR (cm^{-1}): 3168 (OH), 2978 (CH stretching), 1644 (C=N), cm^{-1}; MS (*m/z*%) 445 (M^+, 1.7), 447(M^+ + 2, 0.6), 334 (1), 327 (100), 272 (1), 173 (6), 118 (4), 111 (7), 108 (3), 69 (6), 66 (4); ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.49 (s, 14-H, 1H), 6.78–7.91 (m, 7H, ArH), 9.71 (s, 5-H, 1H), 11.83 (s, 1H, OH); Anal. Calcd for $C_{23}H_{16}ClN_5O_3$; C, 61.96; H, 3.62; N, 15.71. Found: C, 61.70; H, 3.50; N, 16.00.

14-(4-Chlorophenyl)-13-hydroxy-10-methoxy-2-phenyl-14H-[1,2,4]triazolo[2",3": 1',6']pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**10c**): (**a**) Prepared from (**9a**) (0.422 g, 0.001 mol) and benzoyl chloride (0.001 mol) according to the procedure described above to give (**10c**) (0.34 g, 61% yield), which recrystallised from dioxane to give a colourless solid, m.p.285–286 °C; IR (cm^{-1}): 3267 (OH), 3054, 2998, 2850 (CH stretching), 1638 (C=N) cm^{-1}; MS (*m/z*%) 507 (M^+, 1), 509 (M^+ + 2, 0.3), 406 (1), 390 (3), 243 (1), 170 (1), 149 (100), 143(1), 111(7), 77 (5); ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3), 4.50 (s, 14-H, 1H), 6.90–7.96 (m, 12H, ArH), 10.52 (s, 5-H, 1H), 11.86 (s, 1H, OH); Anal. Calcd for $C_{28}H_{18}ClN_5O_3$; C, 66.21; H, 3.57; N, 13.79. Found: C, 66.50; H, 3.40; N, 13.50.

(**b**) A mixture of compound (**9a**) (0.422 g, 0.001 mol), benzaldehyde (0.001 mol), dioxane (20 mL) and piperidine (0.5 mL) was refluxed for 16 h to give (**10c**) (0.45 g, 85% yield) which recrystallised from dioxane as colourless solid.

(**c**) A mixture of compound (**11**) (0.510 g, 0.001 mol), dioxane (20 mL) and piperidine (0.5 mL) was refluxed for 2 h to give (**10c**) (0.44 g, 86% yield) which recrystallised from dioxane as colourless solid.

7-(4-Chlorophenyl)-6-hydroxy-3-methoxy-8-imino-9-phenylmethyleneamino-8,9-dihydro-7H-pyrimido[5',4': 5,6]pyrano[3,2-c]quinoline (**11**): A mixture of compound (**9a**) (0.422 g, 0.001 mol), benzaldehyde (0.001 mol), ethanol (20 mL) and piperidine (0.5 mL) was refluxed for 2 h to give (**11**) (0.42 g, 79% yield), which recrystallised from ethanol to give a yellow solid, m.p.260–261 °C; IR (cm^{-1}): 3434 (OH), 3213 (NH), 3026, 2998, 2944 (CH stretching), 1618 (C=N) cm^{-1}; MS (*m/z*%) 509 (M^+, 0.5), 511 (M^+ + 2, 0.1), 447 (1), 428 (1), 384 (2), 358 (2), 291 (2), 185 (3), 149 (100), 173 (1), 111(9), 97 (10); ^{1}H NMR (DMSO-d_6) δ: 3.37 (s, 3H, OCH_3), 4.57 (s, 7-H, 1H), 8.73 (s, 1H, = HN), 7.52–7.91 (m, 12H, ArH), 8.37 (s, 10-H, 1H), 8.73 (s, 1H, HC=N), 9.14 (b, 1H, NH), 10.03 (s, 1H, OH); Anal. Calcd for $C_{28}H_{20}ClN_5O_3$, C, 65.95; H, 3.95; N, 13.74. Found: C, 65.70; H, 3.80; N, 14.00.

4-(4-Chlorophenyl)-5-hydroxy-8-methoxy-3,4-dihydro-2H-pyrano [3,2-c]quinoline-2-one (**12**): A suspension of compound (**3a**) (0.380 g, 0.001 mol) in ethanolic potassium hydroxide (20%) (25 mL) was heated under reflux for 30 min. The reaction mixture was cooled and neutralised with diluted HCl to give (**12**) (0.25 g, 66% yield), which recrystallised from ethanol to give a colourless solid, m.p.210–211 °C; IR (cm^{-1}): 3072 (OH), 2923, 2854 (CH stretching), 1679 (CO, δ-lactones) cm^{-1}; MS (*m/z*%) 355 (M^+, 16.27), 357 (M^+ + 2, 5.93), 254 (3), 202 (6), 189 (100), 182 (7), 173 (5), 166 (7), 138 (10), 124 (14), 111 (18); ^1H NMR (DMSO-d_6) δ: 2.51, 3.93 (d, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.59 (s, 4-H, 1H), 6.73–7.70(m, 7H, ArH), 11.06 (s, 1H, OH); Anal. Calcd for $C_{19}H_{14}ClNO_4$; C, 64.14; H, 3.97; N, 3.94. Found: C, 63.90; H, 3.80; N, 3.80.

The author acknowledges the help of Quality Control and Propagation of Plants, Department of Botany, Faculty of Girls, Ain Shams University for carrying out the antimicrobial activity.

Received 18 June 2009; accepted 29 July 2009
Paper 09/0646 doi: 10.3184/030823409X12509546260155
Published online: 8 September 2009

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