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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New synthetic approach to coumarino[4,3-*b*]pyridine systems and potential cytotoxic evaluation

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Abstract The reaction of 4-aminocoumarin (**2**) with appropriate α,β-unsaturated ketones gave the corresponding coumarin [4,3-*b*]pyridines. Thus, treatment of **2** with (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one, (1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one, (*Z*)-ethyl 3-(4-chlorophenyl)-2-cyanoacrylate, and (2*E*,6*E*)-2,6-dibenzylidenecyclohexanone (**3**, **6** and **12**) afforded the corresponding coumarino[4,3-*b*]pyridines **5, 7** and coumarino[4,3-*b*] quinoline derivatives **13**, respectively. Heterocyclic annulations of coumarino [5,4-*b*]pyridine system were achieved via reaction of **2** (in situ) with benzylidene derivatives of indandione to give **15** which was also obtained by multicomponent condensation reaction of **2** (in situ) with indandione and benzaldehyde. A representative sample of new synthesized compounds was evaluated as cytotoxic agents.

Keywords Coumarin · Regioselective · Annulation · Biselectrophiles · Cytotoxic activity (in vitro)

Introduction

Coumarins are an important group of heterocyclic compounds due to their important functions in nature and their pharmacological applications. Coumarin constitutes occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted coumarin has played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry (Sun *et al*., 2006; Stachulski *et al*., 2006; Garino *et al*., 2005; Narender *et al*., 2004).

The incorporation of other heterocyclic moiety either as substituent group or as a fused component into parent coumarin alters the property of parent coumarin and converts it into a more useful product (Brahnbhatt *et al*., 2007).

Fused coumarin is interesting due to their significant antibacterial (El-Saghier et *al*., 2007; Okumura *et al*. 1961; Cingolani et al. 1969; Rao *et al*., 1983; El-NaggarA *et al*., 1981; Moustafa, 1991) and novobiocin activities (Kaczka *et al*., 1955). Substituted chromenopyridones were synthesized and evaluated in vitro for the cytotoxic activity against various human cancer cell lines such as prostate (PC-3), breast (MCF-7), CNS (IMR-32), cervix (Hela), and liver (Hep-G2) (Singh *et al*., 2013).

As a result, a number of methodologies have been developed to synthesize coumarin compounds (Shi *et al*., 2003; Kidwai *et al*., 2005; Makarem *et al*., 2008,). Specifically, those bearing a benzopyrone-pyridine or piperidine skeleton were found to interact with DNA (Gutam *et al*., 2009).

Cyclocondensation of enamino skeleton has multiple competing sites for ring-annulation reaction toward the biselectrophiles. The β-position of the exocyclic enamino group is the most nucleophilic and attacks the most electrophilic carbon atom of the reactants with α,β-unsaturated ketones or their synthetic precursor aldehydes and ketones containing at least two active hydrogen atoms are the most widespread and investigated pathways to fused dihydroazaheterocycles (Hamama *et al*., 2007; Chebanov *et al*., 2010; Chebanov and Desenko, 2006), In most cases, both the types of reaction pathways, *i.e*., a sequential protocol involving the initial synthesis of the α,β-unsaturated

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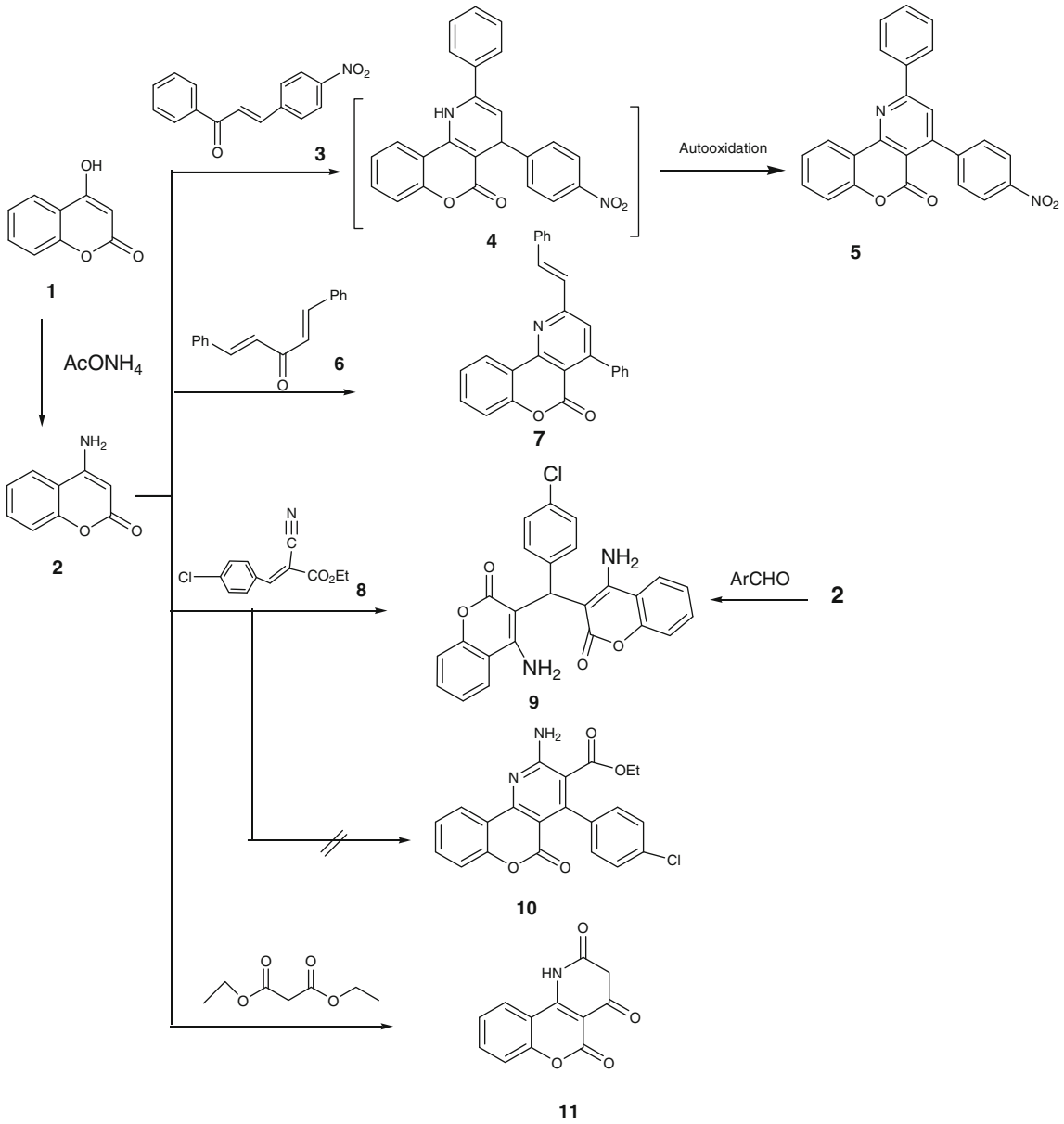


Scheme 1 Pyridine ring formation through nucleophilic attack and cyclization reactions followed by auto-oxidation

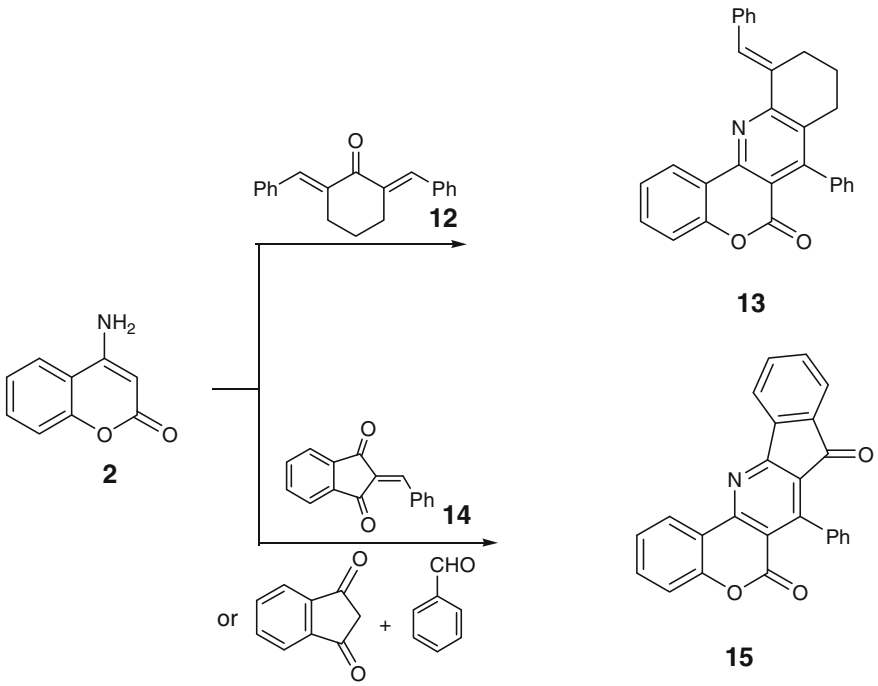
ketonic compounds and the other pathway is the three-component reaction, yield the same products (Lipson *et al*., 2003). However, in rare cases, the direct multicomponent procedure may lead to the formation of different products (Desenko *et al*., 1993). It was felt interesting to synthesize fused heterocyclic systems incorporating coumarin moiety and evaluate their biological activity. Our interest was directed to synthesize pyridine derivatives fused to coumarin rings, which is mainly caused by the known biological activity of these systems (Yamamori *et al*., 1985).

Indandiones are very important synthons for synthesis of fused compounds containing indandione moiety, which are evaluated as inhibitors of human papillomavirus type II (Yoakim *et al*., 2003; Goudreau *et al*., 2007) and as antimicrobial agents (El-Ossaily, 2007).

Results and discussion

Chemistry

4-hydroxycoumarin (Manolov and DanchevN, 1999) (**1**) was reacted with ammonium acetate to give 4-aminocoumarin (**2**) in situ or can be separated in pure form,



Scheme 2 The pyridine ring formation either through reaction of 2 with 2,6-dibenzylidenecyclohexanone or via a multicomponent reaction

which has two competing sites for ring-annulation reaction toward biselectrophiles. One of them is the β-position of the enamino group, and the other site is the amino group itself. Therefore, cyclocondensation reaction of **2** with (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (**3**) in a mixture of ethanol/acetic acid (1:1) furnished the coumarin[4,3-*b*]pyridine derivative **5**. We have found that condensation between **2** and **3** was regioselective. (concordant with similar reactions of aminoisoxazole and bis-electrophiles (Lipson *et al*., 2003) (Scheme 1).

An efficient method for selective synthesis of 2-styrylcoumarino [4,3-*b*]pyridine derivatives **7** was achieved by the Micheal addition of **2** to 1,5-diphenyl-1,4-pentadiene-3-one (**6**) in a mixture of ethanol/acetic acid (1:1) via cyclocondensation reaction through removal of water molecule followed by auto-oxidation. (Scheme 1). Whereas, amino-3-((4-amino-2-oxo-2H-Coumarin-3-yl)(4-chlorophenyl)methyl) -2H-Coumarin-2-one:(**9**) was obtained by the reaction of **2** with ((*E*)-ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (**8**) in ethanol/glacial acetic acid (1:1) instead of the expected coumarino[4,3-*b*]pyridine derivative **10**.

Also, fusion of diethyl malonate with **2** led to 1H-coumarin[4,3-b]pyridine -2,4,5(3H)-trione (**11**) (Scheme 1). In addition, the reaction of **2** with (2E,6E)-2,6-dibenzylidenecyclohexanone (**12**) in DMF afforded (11*E*)-11-benzylidene-8,9,10,11-tetrahydro-7-phenyl-7H-coumarino[4,3-b]quinolin-6(12H)-one (**13**) (Scheme 2). Also, the synthetic potential of compound **2** has been explored for other syntheses through annulation of **2** via one step cyclocondensation reaction with 2-benzylidene-2H-indene-1,3-dione, in ethanol/acetic acid mixture to afford regioselective pentacyclic derivative **15,** indeno [3′,2′:5,6]pyrido[3,2-*c*]coumarin, in high yield (Scheme 2). Similarly, multicomponent condensation reaction of **2** with a mixture of indandione and benzaldehyde led to dihydropyrido[2,3-*a*]inden-5-one derivative **15**.

From the literature survey (Navarrete-Encina *et al*., 2010) synthesized Chromeno[4,3-*b*]pyridine-3-carboxylate derivatives from anisaldehyde derivatives and ethylaminocrotonate.

Assignment of the new synthesized compounds was based on elemental analyses, IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data (*C.f.* "Experimental" Section).r

Biological activity

Effect of drugs on the viability of Ehrlich ascites carcinoma cells (EAC) in vitro

Five coumarino pyridines and its annulated analogues were tested for potential antitumor activity against EAC in vitro (Dashora *et al*., 2011). Results for the IC_{100}, IC_{50}, and IC_{25} values of the active compounds are summarized in Table 1.

The data showed clearly that all the tested compounds showed more toxicity than the 5-FU in vitro studies. Interestingly, compounds **5**, **7**, **9**, **13**, and **15** were increased around three times more toxic than the 5-FU. Experimental potential antitumor activity of the compounds reported in this study to their structures, the following structure activity relationships (SAR's) were postulated: (a) compounds **5** and **7** contain pyridine moiety and this is in agreement with that reported by (Hamama *et al*., 2012). (b) Also, in case of compound **9** and **13**, the high cytotoxic activity may be attributed to the presence of bis-coumarin and quinoline moiety, respectively, which is in agreement with that reported (Gouda *et al*., 2012; Al-Said et *al*., 2011). (c) Moreover, the high cytotoxic activity of compound **15** may be attributed to the presence of indandione moiety; similar results have been reported (Hamama et al., 2012) (Fig. 1).

Table 1 In vitro potential antitumor activity of coumarin analogues using EAC assay

Compound no	Death		
	IC_{100} (μM)	IC_{50} (μM)	IC_{25} (μM)
5-FU	0.77	0.38	0.19
5	0.25	0.12	0.06
7	0.27	0.13	0.06
9	0.25	0.12	0.06
13	0.24	0.12	0.06
15	0.27	0.13	0.06

IC_{100}, IC_{50}, and IC_{25} are the inhibitive concentration at 25, 50, and 100 μM, respectively, of the compounds used. 5-FU is 5-fluorouracil as a well known cytotoxic agent

Conclusions

Modification of coumarin derivatives produced compounds with potential development as anticancer agents. The screening results of compounds **5**, **7**, **9**, **13,** and **15** showed significant activities in certain cancer cells. Additional research, including mode of action studies, is planned to accurately establish relative activity for SAR's and rational design. The cancer chemopreventive effects of coumarin derivatives have been intensively investigated. Coumarin derivatives exhibited pronounced antitumor activities by triggering apoptosis in human tumor cells (Weinman and Ottow, 2007). Studies are underway to investigate the apoptosis-inducing activity of compounds found to be cytotoxic in this study.

Experimental

All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. Elemental analyses were carried out at Micro analytical Center, Faculty of Science, Cairo University. IR spectra were recorded (KBr), (ν cm^{-1}) on a Mattson 5000 FTIR Spectrophotometer at Micro analytical Center Faculty of Science, Mansoura University. ^{1}H NMR Spectra were measured on a Varian Spectrophotometer at 300 MHz, using TMS as an internal reference and DMSO-d_6 or $CDCl_3$ as solvent at Chemistry Department, Faculty of Science, Cairo University. ^{13}C NMR (100 MHz) was recorded in DMSO-d_6 using a Bruker AV 400 spectrometer at Chemistry Department, Faculty of Science, Assiut

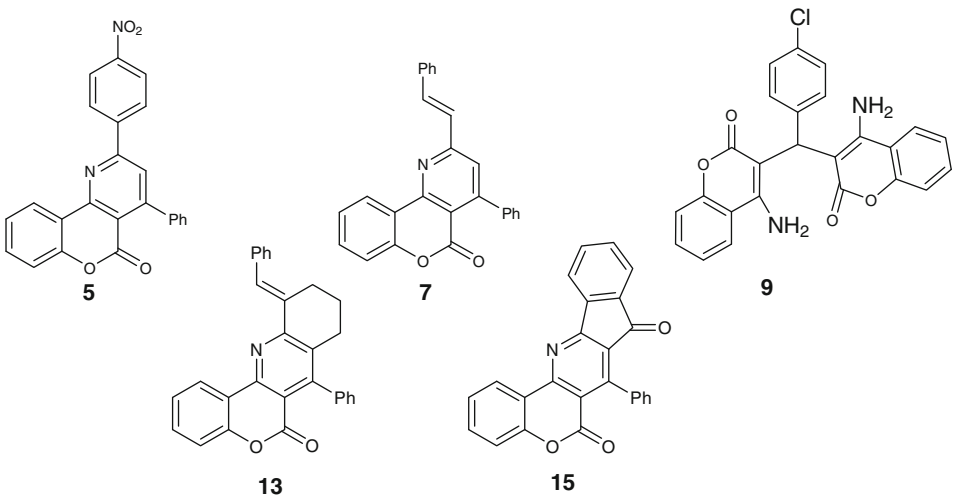


Fig. 1 Structure of the most potent compounds **5**, **7, 9, 13** and **15**

University. Mass spectra were recorded on (Kratos, 70 eV) MS equipment and/or a Varian MAT 311 a Spectrometer, at Microanalytical Center, Faculty of Science, Cairo University. Reaction mixtures were monitored by thin layer chromatography using EM science silica gel-coated plates with visualization by irradiation with ultraviolet lamp. Biological testing was carried out at Drug Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

2-(4-Nitrophenyl)-4-phenyl-5H coumarino[4,3-b]pyridin-5-one (**5**)

A mixture of **1** (0.3 g, 1.85 mmol) and ammonium acetate (0.28 g, 3.64 mmol) in ethanol/glacial acetic acid (20 ml; 1:1) was refluxed for 4 h. (E)-3-(4-Nitro phenyl)-1-phenylprop-2-en-1-one (**3**) (0.47 g, 1.85 mmol) was then added and further refluxed for 7 h. After cooling, the reaction mixture was poured onto ice and allowed to stand at room temperature. The formed precipitate was filtered off, washed with water, and recrystallized from methanol to give product **5**.

Yield 58 % (yellowish brown crystals); m.p. 120–121 °C (methanol); $R_f = 0.65$[pet. ether (60–80): ethyl acetate (3:2)]; IR (KBr): $\nu/cm^{-1} = 1668$ (O–C=O),1610 (C=N); ^{1}H NMR (DMSO-d_6) δ: 7.97 (d, $J = 8.4$ Hz, 6H, $CH_{Ar\ a}$),7.78 (t, 2H, $CH_{Ar\ b}$),7.43–7.62 (m, 6H, 5H CH_{Ar} + 1H pyridine; ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 106.7 (C-3), 116.1 (C-4a), 123.1 (2CHAr), 123.5 (CHAr), 123.9 (CHAr), 125.5 (2CHAr), 126.1 (CHAr), 127.9 (CHAr), 128.9 (2CHAr), 132.1 (2CHAr), 133.5 (C-10a), 136.4(CAr), 137.1(CAr), 141.2 (CAr), 145.8 (CAr), 148.1 (C-10b), 150.9 (C-6a), 152.1 (C-4), 158.2 (C-5), 161.1 (C-2); MS (EI, 70 eV) *m/z* (%) = 395 (M^++1, 1.7), 380 (1.3), 303 (1.0), 259 (1.2), 253 (37.5), 237 (5.0), 236 (19.5), 223 (4.6),221 (1.4),207 (9.8), 206 (23.7),178 (22.2), 162 (15.6), 159 (1.2), 122 (6.4), 121 (18.8),120 (33.8),105 (57.9), 92 (40.0), 77 (100.0, base peak); Anal. Calcd. for $C_{24}H_{14}N_2O_4$ (394.09) : C, 73.09; H, 3.58; Found: C, 73.03; H, 3.62.

4-Phenyl-2-styryl-5H-coumarino [4,3-b]pyridin-5-one (**7**)

A mixture of **1** (0.3 g, 1.85 mmol) and ammonium acetate (0.28 g, 3.64 mmol) in ethanol/glacial acetic acid (20 ml; 1:1) was refluxed for 4 h.; then dibenzalacetone (0.29 g, 1.85 mmol) was added and further refluxed for 7 h. After cooling, the mixture was poured onto ice and allowed to stand at room temperature. The formed precipitate was filtered off, washed with water, and recrystallized from methanol to give product **7**.

Yield 76 % (pale brown powder); m.p. 96–98 °C (methanol); $R_f = 0.65$ [pet. ether (60–80): ethyl acetate (3:2)]; IR (KBr): $\nu/cm^{-1} = 1677$ (O–C=O),1602 (C=N); ^{1}H NMR ($CDCl_3$) δ:6.61(d, 1H, $J = 8$ Hz, CH_{Ar}), 6.93 (d, 1H, $J = 8$ Hz, CH=C$\underline{H}_{Ar}$,) 6.81–7.99 (m, 10H, CH_{Ar}); MS (EI, 70 eV) *m/z* (%) = 377 (M^++2, 2.7), 376 (M^++1,3.95), 375 (M^+, 4.22), 374 (M^+−1, 9.6), 300 (2.8), 298 (8.4), 272 (2.8), 249 (30.2), 223 (6.7), 195 (3.5), 191 (12),178 (17.6), 162 (14.0), 121 (77.8), 103 (59.2), 92 (88.1),77 (100.0, base peak); Anal. Calcd. for $C_{26}H_{17}NO_2$ (375.42): C, 83.18; H, 4.56; Found: C, 83.09; H, 4.50.

4-Amino-3-((4-amino-2-oxo-2H-coumarin-3-yl) (4-chlorophenyl) methyl)-2H-Coumarin-2-one (**9**)

A mixture of **2** (0.3 g, 1.85 mmol) and (E)-ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (0.44 g, 1.85 mmol) in ethanol/glacial acetic acid (20 ml; 1:1) was refluxed for 9 h. White flakes of product was formed during reflux. After cooling, the mixture was poured onto ice and allowed to stand. The formed precipitate was filtered off, washed with water, and recrystallized from ethanol to give product **9**.

Yield 70 % (white sheet); m.p. >300 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ:8.08 (d, 4H, $J = 7.8$ Hz, $H_{Ar\ a}$), 7.72 (s, 1H, CH), 7.67 (t, 4H, $H_{Ar\ b}$),7.33 (d, 2H $J = 8.7$ Hz, $2H_c$), 7.13 (d, 2H $J = 8.4$ Hz, $2H_d$), 5.91 (s, 4H, $2NH_2$): ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.9 (CH), 94.1(2C-3), 114.5 (2CAr), 116.8 (2C-4a), 123.9 (2C-8), 127.9(2C-6), 128.5(2C-7), 130.1(2CHAr), 1316 (CHAr), 132.4(2CHAr), 137.2(CAr), 152.1(2C-8a), 154.2 (2C-4), 163.9(2C-2); MS (EI, 70 eV) *m/z* (%) = 400 (M^++5, 4.9), 399 (M^++4, 8.3), 284 (36.8), 283(59), 282 (91.7), 281(100, base peak), 280 (25), 161 (93.8), 160 (54.9),121 (17.4), 112 (29.2), 111(15.3),77(54.9); Anal. Calcd. for $C_{25}H_{18}N_2O_4$ (410.42): C, 73.16; H, 4.42; Found: C, 73.09; H, 4.38.

1H-Coumarino [4,3-b]pyridine-2,4,5(3H)-trione (**11**)

A mixture of **2** (0.3 g, 1.85 mmol) and diethyl malonate (0.32 g, 1.85 mmol) was fused in oil bath at 180 °C for 6 h. The formed precipitate was washed with ethanol, filtered off to give product **11** which was washed by boiling in ethanol.

Yield 73 % (deep brown crystals); m.p. >300 °C (ethanol); $R_f = 0.54$ [pet. ether (60–80): ethyl acetate (3:2)]; IR (KBr): $\nu/cm^{-1} = 3392$ (NH), 1690 (true C=O), 1647, 1614 (C=O),1559 (C=N); MS (EI, 70 eV) *m/z* (%) = 230 (M^++1, 13.8), 229 (M^+, 100.0, base peak), 228 (M^+−1, 5.6), 200 (48.4), 199 (3.1), 160 (1.7), 146 (16.6), 145(38.1), 113(1.7), 77 (10.5), 53(18.9). Anal. Calcd. for $C_{12}H_7NO_4$ (229.19): C, 62.89; H, 3.08; Found: C, 62.81; H, 3.17.

*(E)-11-Benzylidene-8,9,10,11-tetrahydro-7-phenylcoumarino[4,3-b]quinolin-6-one (**13**)*

A mixture of **2** (0.3 g, 1.85 mmol) and dibenzylidene cyclohexanone (0.5 g, 1.85 mmol) in DMF (20 ml) was refluxed for 30 h. Cooling the reaction mixture then poured onto ice cold water. The formed precipitate was filtered off, washed with water, and recrystallized using ethanol to give product **13**.

Yield 73 % (deep brown crystals). m.p. 76–78 °C (ethanol); $R_f = 0.79$ [pet. ether (60–80): ethyl acetate (3:2)]; IR (KBr): $\nu/cm^{-1} = 1626$ (O–C=O),1608 (C=N); ^1H NMR ($CDCl_3$) δ:1.56 (m, 2H, CH_2), 1.9 (t, 2H, CH_2), 6.60 (s,1H, C=C$\underline{H}_{Ar}$), 6.97–7.98 (m, 14H, CH_{Ar}); MS (EI, 70 eV) *m/z* (%) = 418.1(M^++3, 14.5), 388 (2.7), 342 (12.5), 341 (43.5), 327 (5.4), 287 (3.0), 263 (3.8), 249 (18.6), 213 (6.3), 162 (9.9), 144 (2.7), 129.2 (19.7), 122 (8.6) 107 (4.4), 92 (48.1), 91 (69.1), 89 (20.5), 77 (100.0, base peak); Anal. Calcd. for $C_{29}H_{21}N\ O_2$ (415.48): C, 83. 83; H, 5.09; Found: C, 83.76; H, 5.01.

Reaction of 4-aminocoumarin with arylidene of indandione (15)

(a) A mixture of **1** (0.3 g, 1.85 mmol) and ammonium acetate (0.28 g, 3.64 mmol) in ethanol/glacial acetic acid (20 ml; 1:1) was refluxed for 4 h. The arylidene of indandione **14** (0.43 g, 1.85 mmol) was added then further refluxed for 1 h, whereby yellow needles of product **15** were formed.

(b) A mixture of **1** (0.3 g, 1.85 mmol) and ammonium acetate (0.28 g, 3.64 mmol) in ethanol/glacial acetic acid (20 ml; 1:1) was refluxed for 4 h.; then indandione (0.27 g, 1.85 mmol) followed by benzaldehyde (0.19 g, 1.85 mmol) were added and further refluxed until a violet color disappeared after (1 h); then yellow needles of product **15** were formed.

Yield 73 %/81 % (yellow needles); m.p. 286–288 °C (chloroform); $R_f = 0.78$ [pet. ether (60–80): ethyl acetate (3:2)]; IR (KBr): $\nu/cm^{-1} = 1712$ (C=O), 1668 (O–C=O) 1544 (C=N); ^1H NMR (DMSO-d_6) δ: 7.99 (d, $J = 7.2$ Hz, 4H, $CH_{Ar\,a}$),7.78 (t, 4H, $CH_{Ar\,b}$),7.43–7.62 (m, 5H, CH_{Ar}); MS (EI, 70 eV) *m/z* (%) = 375 (M^+, 9.2), 374(M^+-1, 8.8), 359 (90.7), 358(22.3), 301 (12.2), 244(13.5), 198 (48), 161(11.7), 154 (19.2), 124 (20.6), 108 (17.4), 93 (56.9), 90 (45.7),78 (21.4), 77 (100, base peak); Anal. Calcd. for $C_{25}H_{13}NO_3$ (375.38): C, 79.99; H, 3.49; Found: C, 79.92; H, 3.41.

Antitumor activity

Cytotoxic evaluation of the tested compounds

Ehrlich ascites carcinoma cells were obtained from National Cancer Institute, Cairo, Egypt. To examine whether the synthesized compounds have a direct cytotoxic effect on Ehrlich ascites carcinoma cells (Dashora *et al.*, 2011), viability was estimated by the trypan blue (Sheeja *et al.*, 1997), exclusion test. The desired concentration of tumor cells (2×10^6 cells per 0.2 ml) was obtained by dilution with saline solution (0.9 % sodium chloride). Viability of tumor cells obtained and used in this experiment was always higher than 90 %. Below this percentage, the cells were discarded and the entire procedure was repeated.

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