Synthesis of Some Coumarin Hybrids and Evaluating their Anticancer Activity

Ehab Abdel-Latif*, Mohamed Mahmoud Abou-Elzahab, Mona E. Ibrahim, Nivien E. Maarouf, Mamdouh Abdel-Mogib
Department of Chemistry, Mansoura University, Mansoura, Egypt

Corresponding author: Ehab Abdel-Latif, Department of Chemistry, Mansoura University, Mansoura 35516, Egypt. Tel: +201002529365; Email: ehabattia00@gmx.net


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Abstract

Coumarin-chalcone hybrids 3a and 3b were utilized as versatile precursor for the synthesis of coumarinyl-pyridine and coumarinyl-pyrimidine hybrids. The reaction of chalcones 3 with malononitrile or ethyl cyanoacetate proceeded in hot glacial acetic acid and ammonium acetate to afford the coumarinyl 2-aminonicotinonitriles 4 and coumarinyl 2-hydroxynicotinonitriles derivatives 5, respectively. Heating of chalcone derivatives 3 with thiourea in refluxing sodium ethoxide furnished the corresponding coumarinyl-pyrimidines 6. Condensation of coumarinyl-acetohydrazide scaffold 7 various aromatic aldehydes afforded the corresponding acrylohydrazides 8 which underwent heterocyclization with malononitrile furnished the coumarinyl-pyridinone derivatives 9. The constructed coumarin scaffolds were evaluated in vitro for their anticancer activity via the standard MTT method versus Hepatocellular Carcinoma (HepG2) and breast cancer (MCF-7).

Keywords: 3-Acetylcoumarin; Breast Cancer; Coumarinyl 2-Aminonicotinonitriles; Isovanillin; Malononitrile

Introduction

Coumarin scaffolds display wide range of pharmaceutical properties with low toxicity. They were described as anticancer [1-4], antioxidant [4,5], anticoagulant [6], anti HIV [7,8], antimicrobial [9,10] and anti-inflammatory [11] agents. The reported cytotoxic activity of these coumarins versus various cell lines is attributed to the inhibition of the cellular proliferation via different mechanisms such as inhibition of the telomerase enzyme [12], inhibition of protein kinase activity and down regulation of oncogene expression [13] or by inducing the caspase-9 mediated apoptosis [14]. In addition, coumarin derivatives exhibited high ability to suppress cancer cell proliferation by arresting cell cycle in G0/G1 [12] and G2/M phases [15]. These findings make coumarin derivatives (Figure 1), promising scaffolds for cytotoxic hybrids framework.

Chalconoid compounds, as examples of α,β-unsaturated carbonyl class, are utilized to inhibit cancer and have comprehensive cytotoxic potential in several models [16] (Figure 1). It has been reported in the literature that hydrazide-hydrazide scaffolds (-CO-NH-N=CH-) [17-19], acrylonitrile [20] and/or 2-amino-nicotinonitrile moieties [21] display important antitumor activity (Figure 1).

In the present research, we focused on hybridization strategy to combine coumarin nucleus with three biologically active molecules; pyridine, pyrimidine and acryl hydrazide in an attempt to find bioactive pharmacophores. 3-Acetylcoumarin (1) was utilized as versatile precursor for the synthesis of chalcones and their corresponding pyridine, pyrimidine and acrylhydrazide derivatives. 3-Acetylcoumarin has been synthesized according to the reported literature procedure [26] from salicylaldehyde, and equimolar amount of ethyl acetoacetate.
Thus, our strategy in this work starts by the synthesis of coumarin-chalcone hybrids containing different substituents in the aromatic rings that can potentially be used as new lead compounds in drug discovery, particularly as anticancer agents. Coumarin-chalcone hybrids $3a$ [27] and $3b$ were prepared by Claisen-Schmidt reaction of 3-acetylcoumarin (1) with substituted aromatic aldehydes 2 (namely; 4-nitrobenzaldehyde and isovanillin). The reaction has been achieved by refluxing the reactants in ethyl alcohol and piperidine as catalyst.

The 2-aminonicotinonitrile derivatives $4a$ [28] and $4b$ were synthesized through the reaction of chalcone scaffolds $3$ with malononitrile in refluxing glacial acetic acid containing ammonium acetate (Scheme 2). Spectroscopic techniques ($^1$H NMR, IR and MS) was employed to secure the structures of these synthesized 2-aminonicotinonitrile scaffolds. (cf. experimental)
A plausible mechanism for the reaction of chalcones 3 with malononitrile is indicated in Figure (2). The reaction passes through addition of malononitrile and ammonia to the δ,β-unsaturated system to afford intermediate 4-i, which underwent tautomerization into amino form 4-ii. Intramolecular cyclization of 4-ii proceeded via nucleophilic addition of the amino function to the nitrile group to form the imino-tetrahydropyridine 4-iii, which underwent tautomerization into amino-dihydropyridine 4-iv. Autoxidation of this dihydropyridine 4-iv promoted the loss of hydrogen molecule with the formation of pyridine compound 4.

The 2-hydroxynicotinonitrile derivatives 5a and 5b were constructed through the reaction of chalcone scaffolds 2 with ethyl cyanoacetate in refluxing glacial acetic acid containing ammonium acetate (Scheme 3). Spectroscopic techniques (IR, 1H NMR and MS) was employed to secure the structures of these synthesized 2-hydroxynicotinonitrile scaffolds. The presence of infrared absorptions, in the spectrum of 5a, at 3408 and 3376 cm⁻¹ refers to the N-H and O-H functions. The stretching absorptions at 2216 and 1736 cm⁻¹ clearly indicates the presence of nitrile and carbonyl functions. 1H NMR spectrum of 5a revealed, in addition to the multiplet signal of eight aromatic protons, two singlet signals at 7.24 and 8.70 ppm for the protons of pyridine C-5 and coumarin C-4, respectively. The singlet at 12.64 ppm indicated the proton of hydroxyl group.
A plausible mechanism for the reaction of chalcones 3 with malononitrile is indicated in (Figure 3). The reaction passes through addition of ethyl cyanoacetate and ammonia to the δ,β-unsaturated system to afford intermediate 5-i, which underwent tautomerization into amino form 5-ii. Intramolecular cyclization of 4-ii proceeded via nucleophilic addition of the -NH$_2$ function to the C=O group followed by loss of ethanol molecule to form the tetrahydropyridone 5-iii, which underwent tautomerization into hydroxy-dihydropyridine 5-iv. Autoxidation of this dihydropyridine 5-iv promoted the loss of hydrogen molecule with the formation of pyridine compound 5.

The reaction of chalcone derivatives 3 with thiourea has been carried out by refluxing in ethanolic solution of C$_2$H$_5$ONa to furnish the corresponding aryl coumarinyl-pyrimidines 6a and 6b (Scheme 4). Spectroscopic techniques (IR, $^1$H NMR and MS) was employed to secure the structures of these synthesized coumarinyl-pyrimidine scaffolds. The infrared spectrum of 6b displayed absorption bands at 3415, 3394 and 3213 cm$^{-1}$ for the (NH and OH) functions in addition to 1717 cm$^{-1}$ for the (C=O) group. The $^1$H NMR spectrum of 6b showed signals at 3.81 ppm (s, 3H, OCH$_3$), 4.78 ppm (d, 1H, H-6 of pyrimidine), 6.50 ppm (d, 1H, H-5 of pyrimidine), 6.88-7.76 ppm (m, 7H, aromatic-H), 8.39 ppm (s, 1H, H-4 of coumarin), 9.10 ppm (s, 1H, NH), 9.55 ppm (s, 1H, OH) and 9.72 ppm (s, 1H, NH).
The plausible reaction mechanism was indicated in Figure (4), the reaction is initiated by base-mediated aza-Michel addition of thiourea to chalcones 3 to form the Michel adduct 6-i. The amino group of intermediate 6-i underwent intramolecular attacked on the carbonyl function to give the intermediate 6-ii, followed by loss water molecule gave the target aryl coumarinyl-pyrimidine product 6.

Condensation of 1 with cyanoacetic acid hydrazide in methyl alcohol containing drops of glacial CH$_3$COOH furnished the corresponding acetohydrazide scaffold 7 [29], which underwent subsequent condensation with various aromatic aldehydes by heating in ethyl alcohol containing three drops of piperidine to afford the corresponding acrylohydrazide compounds 8a and 8b (Scheme 5). To explore the synthetic potentially of compounds 8a and 8b, the reactivity of 8 towards Michael addition with malononitrile as a possible synthetic route to get pyridinone derivatives 9 was examined. Compounds 9a and 9b were achieved by refluxing compounds 8a and 8b with malononitrile and triethylamine in ethyl alcohol. Elucidation of the new synthesized derivatives 9a and 9b was based on elemental analysis, IR, $^1$H NMR and mass spectroscopy (cf. Experimental Section).
Biological Evaluation (Anti-cancer activity)

The constructed seventy coumarin scaffolds were evaluated in vitro for their anticancer activity via the standard MTT method [30-32] versus two human tumor cell lines; Hepatocellular Carcinoma (HepG2) and breast cancer (MCF-7). Doxorubicin has been used as standard anticancer drug for comparison. MTT assay is a standard colorimetric assay for measuring the inhibit effects of compounds on cell growth.

Yellow MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide is reduced to purple formazan derivative by mitochondria succinate dehydrogenase of viable cells. The absorbance of this colored formazan solution in DMSO is measured and recorded at certain wave length 570 nm by using a plate reader (EXL 800, USA). the relative cell viability in percentage was calculated as (A570 of treated sample / A570 of untreated samples) x 100.

The results of anticancer activity of the chalconoid compounds are depicted in (Table 1). They revealed that compounds 7, 8b and 5b exhibited the highest cytotoxic activity against the tested cell lines HepG2 and MCF-7. Their IC\textsubscript{50} values (ranges from 5.81 to 11.26 µM) were very close to the reference drug (Doxorubicin, IC\textsubscript{50} = 4.17-4.50 µM).

The coumarin compound 9b showed strong cytotoxic activity with the percentage viability IC\textsubscript{50} at 13.68 and 17.01 µM for the hepatocellular carcinoma (HepG2) and the breast cancer (MCF-7), respectively. The coumarin-chalconoid compound 3b, substituted with methoxy and hydroxy groups at the benzene ring, displayed moderate inhibitory activity for both cell lines (HepG2 and MCF-7) with the percentage viability IC\textsubscript{50} at 22.96 and 29.54 µM, respectively. The coumarinyl-nicotinonitrile compound 4b displayed also moderate inhibitory activity against HepG2 and MCF-7 with the percentage viability IC\textsubscript{50} at 28.60 and 24.89 µM, respectively.

Structure Activity Relation (SAR)

In an attempt to find a relationship between the Structure and their Anticancer Activity (SAR), we can assume that the presence of methoxy group in the skeleton of chalcone is responsible for the broad spectrum of anti-cancer activity towards the tested cell lines (HepG2 and MCF-7) and makes the compounds very stronger as anti-cancer agents. This assumption finds support from the results (Table 1), the anticancer activity of the chalconoid compounds substituted (3b, 4b, 5b, 6b, 8b and 9b) with methoxy at the para-position and hydroxy group at the meta-position of the benzene ring is higher than its corresponding chalconoid compounds (3b,
4b, 5b, 6b, 8b and 9b) substituted with nitro group at the para-position of the benzene ring.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>In vitro Cytotoxicity IC₅₀ (µM)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HepG2</td>
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<tr>
<td>DOX</td>
<td>4.50±0.3</td>
</tr>
<tr>
<td>3a</td>
<td>31.23±2.4</td>
</tr>
<tr>
<td>3b</td>
<td>22.96±1.8</td>
</tr>
<tr>
<td>4a</td>
<td>63.49±3.7</td>
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<tr>
<td>4b</td>
<td>28.60±2.1</td>
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<tr>
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<td>60.48±3.6</td>
</tr>
<tr>
<td>5b</td>
<td>9.24±1.0</td>
</tr>
<tr>
<td>6a</td>
<td>56.73±3.4</td>
</tr>
<tr>
<td>6b</td>
<td>46.41±3.0</td>
</tr>
<tr>
<td>7</td>
<td>5.81±0.4</td>
</tr>
<tr>
<td>8a</td>
<td>39.76±2.7</td>
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<tr>
<td>8b</td>
<td>7.73±0.8</td>
</tr>
<tr>
<td>9a</td>
<td>38.12±2.6</td>
</tr>
<tr>
<td>9b</td>
<td>13.68±1.2</td>
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</tbody>
</table>

* IC₅₀ (µM): 1-10 (very strong), 11-20 (strong), 21-50 (moderate), 51-100 (weak) and higher than 100 (non-cytotoxic). DOX (Doxorubicin)

Table 1: Cytotoxicity activity of the synthesized coumarin scaffolds versus HepG2 and MCF-7.

**Experimental**

**General Remarks**

Melting points (uncorrected) have been determined on Gallenkamp electric apparatus. IR spectra were registered on a Nicolet 5000 FT-IR spectrophotometer. The ¹H NMR and ¹³C NMR spectra were obtained by JEOL’s NMR spectrometer (500 MHz) in DMSO-d₆. Mass analyses were registered on Quadrupole GC/MS Thermo Scientific Focus/DSQII at 70 eV. Elemental analyses (C, H and N) were determined on Perkin Elmer 2400 analyzer.

**Synthesis of coumarin-Chalcone hybrids 3a and 3b**

To a well-stirred suspension of 3-acetylcoumarin (0.02 mol) in ethyl alcohol, 4-nitrobenzaldehyde or isovanillin (0.02 mol) and few drops of piperidine were added. The mixture was refluxed for 6 hours and the resulting solid was picked up by filtration and recrystallized via boiling in MeOH.

1-(Coumarin-3-yl)-3-(4-nitrophenyl)-prop-2-en-1-one (3a)

Yellow powder, yield = 78%, m.p. 265-266°C, lit. m.p. 267°C [27]. IR (ν_max/cm⁻¹): 1671 (C=O, conjugated), 1723 (C=O, coumarin). ¹H NMR (DMSO-d₆): δ_H (1H, J = 8.50 Hz), 7.40-7.81 (m, 4H), 7.94 (d, 1H, J = 8.50 Hz), 8.05 (d, 2H, J = 8.80 Hz), 8.24 (d, 2H, J = 8.40 Hz), 8.60 (s, 1H). Analysis for C₈H₁₆NO₅ (321), Calcd: C, 67.29; H, 3.45; N, 4.36%. Found: C, 67.16; H, 3.49; N, 4.28%.

1-(Coumarin-3-yl)-3-(3-hydroxy-4-methoxyphenyl)-prop-2-en-1-one (3b)

Yellow powder, yield = 72%, m.p. 218-219°C. IR (ν_max/cm⁻¹): 3435 (O-H), 1676 (C=O, conjugated), 1722 (C=O, coumarin), 1608 (C=C). ¹H NMR (DMSO-d₆): δ_H (3H, 1H, J = 8.40 Hz), 7.00 (d, 1H, J = 8.60 Hz). 7.08 (d, 1H, J = 8.50 Hz), 7.18 (s, 1H), 7.41-7.82 (m, 4H), 7.84 (d, 1H, J = 8.50 Hz), 8.61 (s, 1H), 9.48 (s, 1H). Analysis for C₉H₁₈NO₅ (322), Calcd: C, 70.80; H, 4.38%. Found: C, 70.96; H, 4.44%.

**Synthesis of 2-amino-4-aryl-6-(coumarin-3-yl)-nicotinonitriles 4a and 4b**

A solution of coumarin-chalcone hybrids 3a or 3b (0.003 mol), malononitrile (0.006 mol) and ammonium acetate (1.2 mol) in glacial acetic acid (15 mL) was refluxed for 6 hours. After cooling, 15 mL water was added to the reaction mixture and the solid that formed was collected by filtration. Recrystallization was carried out from AcOH/H₂O to furnish the corresponding nicotinonitriles 4a and 4b.

2-Amino-4-(4-nitrophenyl)-6-(coumarin-3-yl)-nicotinonitrile (4a)

Yellow powder, yield = 70%, m.p. 250-251°C, lit. m.p. 252-254°C [28]. IR (ν_max/cm⁻¹): 3456, 3365 (NH₃), 2212 (C=N), 1721 (C=O). ¹H NMR: δ_N (2H, J = 8.40 Hz), 7.34 (d, 1H, J = 8.50 Hz), 8.76 (s, 1H), 8.76 (s, 1H). MS (EI, m/z): 350 (M⁺, 100%). Analysis for C₂₄H₁₉N₃O₄ (384), Calcd: C, 65.63; H, 3.15; N, 14.58%. Found: C, 65.46; H, 3.21; N, 14.47%.

2-Amino-4-(3-hydroxy-4-methoxyphenyl)-6-(coumarin-3-yl)-nicotinonitrile (4b)

Yellow powder, yield = 66%, m.p. 257-258°C. IR (ν_max/cm⁻¹): 3432, 3378 (NH₃ and O-H), 2218 (C=N), 1727 (C=O). ¹H NMR: δ_N (3H, 3H, J = 8.50 Hz), 8.76 (s, 1H), 8.72 (s, 1H), 8.54 (s, 1H). MS (EI, m/z): 350 (M⁺, 71.6%). Analysis for C₂₄H₁₉N₃O₄ (384), Calcd: C, 68.57; H, 3.92; N, 10.90%. Found: C, 68.69; H, 3.96; N, 10.96%.

**Synthesis of 2-hydroxy-4-aryl-6-(coumarin-3-yl)-nicotinonitriles 5a and 5b**

A solution of coumarin-chalcone hybrids 3a or 3b (0.003 mol),...
ethyl cyanoacetate (0.006 mol) and ammonium acetate (1.2 mol) in glacial acetic acid (15 mL) was refluxed for 6 hours. After cooling, the reaction mixture was diluted with 15 mL water and the solid that formed was collected by filtration, dried and recrystallized from AcOH/H₂O to furnish the corresponding nicotinonitriles 5a and 5b.

2-Hydroxy-4-(4-nitrophenyl)-6-(coumarin-3-yl) nicotinonitrile (5a)

Brown powder, yield = 62%, m.p. 284-284°C. IR (ν_max/cm⁻¹): 3408, 3376 (NH and OH), 2216 (C=O), 1675 (C=O, amide). 1H NMR: δ_H (ppm) 7.24 (s, 1H), 7.35-7.89 (m, 8H), 8.70 (s, 1H), 12.64 (s, 1H). MS (EI, m/z): 386 (M⁺, 48.3%). Analysis for C_{21}H_{17}N_{2}O_{5} (386), Calcd: C, 62.69; H, 3.51; N, 10.54%. Found: C, 63.15; H, 4.24; N, 7.36%. Caled: C, 63.31; H, 4.17; N, 7.46%.

Preparation of 2-cyano-N’-(1-(coumarin-3-yl) ethylidene)-acetohydrazide (7)

To a solution of cyanoacetic acid hydrazide (0.01 mol) in methyl alcohol (30 mL), 3-acetyl-coumarin (0.01 mol, 2.18 g) and 1 mL CH₂COOH were added. The reaction was completed after reflux for 2 hours and then the solid that formed was filtered, and recrystallized from EtOH/CHCl₃ mixture (1:1).

Yellow crystals, yield = 80%, m.p. 171-173°C, lit. m.p. 172°C [29]. IR (ν_max/cm⁻¹): 3193 (NH), 2227 (C=O), 1691 (C=O, amide), 1722 (C=O, coumarin). 1H NMR: δ_H (ppm) 2.22 (s, 3H), 4.18 (s, 2H), 7.32-7.91 (m, 4H), 8.82 (s, 1H), 11.06 (s, 1H). MS (EI, m/z): 402 (M⁺, 46.7%). Analysis for C_{28}H_{17}N_{2}O_{5} (402), Calcd: C, 62.69; H, 3.51; N, 13.92%. Found: C, 62.51; H, 3.58; N, 13.81%.

Preparation of 2-cyano-3-aryl-N’-(1-(coumarin-3-yl)-ethylidene)-acrylohydrazide 8a and 8b

To a solution of 7 (0.005 mol) and 4-nitrobenzaldehyde or isovanillin (0.005 mol) in ethyl alcohol (30 mL), three drops of piperidine were added. The reaction was completed after reflux for 2 hours. The solid that obtained while hot was picked up by filtration, dried and recrystallized from ethyl alcohol. 2-Cyano-3-(4-nitrophenyl)-N’-(1-(coumarin-3-yl)-ethylidene)-acrylohydrazide (8a)

Yellow crystals, yield = 81%, m.p. 204-205°C. IR (ν_max/cm⁻¹): 3446 (NH), 2227 (C=O), 1721 (C=O, coumarin), 1681 (C=O, amide). 1H NMR: δ_H (ppm) 2.17 (s, 3H), 7.45-8.14 (m, 8H), 8.34 (s, 1H), 8.62 (s, 1H), 11.48 (s, 1H). MS (EI, m/z): 402 (M⁺, 46.7%). Analysis for C_{28}H_{17}N_{2}O_{5} (402), Calcd: C, 62.69; H, 3.51; N, 13.92%. Found: C, 62.51; H, 3.58; N, 13.81%.

2-Cyano-3-(3-hydroxy-4-methoxyphenyl)-N’-(1-(coumarin-3-yl)-ethylidene) acrylohydrazide (8b)

Yellow crystals, yield = 77%, m.p. 158-160°C. IR (ν_max/cm⁻¹): 3439 (NH and OH), 2221 (C=O), 1675 (C=O, amide). 1H NMR: δ_H (ppm) 2.19 (s, 3H), 3.82 (s, 1H), 6.98-7.80 (m, 7H), 8.18 (s, 1H), 8.68 (s, 1H), 9.58 (s, 1H), 11.64 (s, 1H). MS (EI, m/z): 403 (M⁺, 26.1%). Analysis for C_{22}H_{16}N_{2}O_{5} (403), Calcd: C, 65.50; H, 4.25; N, 10.42%. Found: C, 65.28; H, 4.32; N, 10.54%.

Synthesis of 6-amino-4-aryl-2-oxo-1-((1-(coumarin-3-yl)-ethylidene) acrylohydrazide

Yellow crystals, yield = 80%, m.p. 171-173°C, lit. m.p. 172°C [29]. IR (ν_max/cm⁻¹): 3193 (NH), 2227 (C=O), 1691 (C=O, amide), 1722 (C=O, coumarin). 1H NMR: δ_H (ppm) 2.22 (s, 3H), 4.18 (s, 2H), 7.32-7.91 (m, 4H), 8.82 (s, 1H), 11.06 (s, 1H). MS (EI, m/z): 402 (M⁺, 46.7%). Analysis for C_{28}H_{17}N_{2}O_{5} (402), Calcd: C, 62.69; H, 3.51; N, 13.92%. Found: C, 62.51; H, 3.58; N, 13.81%.

2-Cyano-3-(3-hydroxy-4-methoxyphenyl)-N’-(1-(coumarin-3-yl)-ethylidene) acrylohydrazide (8b)

Yellow crystals, yield = 77%, m.p. 158-160°C. IR (ν_max/cm⁻¹): 3439 (NH and OH), 2221 (C=O), 1675 (C=O, amide). 1H NMR: δ_H (ppm) 2.19 (s, 3H), 3.82 (s, 1H), 6.98-7.80 (m, 7H), 8.18 (s, 1H), 8.68 (s, 1H), 9.58 (s, 1H), 11.64 (s, 1H). MS (EI, m/z): 403 (M⁺, 26.1%). Analysis for C_{22}H_{16}N_{2}O_{5} (403), Calcd: C, 65.50; H, 4.25; N, 10.42%. Found: C, 65.28; H, 4.32; N, 10.54%.

Synthesis of 6-amino-4-aryl-2-oxo-1-((1-(coumarin-3-yl)-ethylidene) amino)-1,2-dihydropyridine-3,5-dicarbonitrile 9a and 9b

To a well-stirred suspension of acrylohydrazide 8 (0.002 mol) in 30 mL ethyl alcohol, malononitrile (0.002 mol) and 0.5 mL of triethylamine were added. The reaction was completed after refluxing the reactants for 4 hours and then cooled to 25°C. The solid that formed was picked up by filtration and recrystallized from ethyl alcohol.
6-Amino-4-(4-nitrophenyl)-2-oxo-1-((1-coumarin-3-yl)-ethylidene)-amino)-1,2-dihydropyridine-3,5-dicarbonitrile (9a)

Brown powder, yield = 68%, m.p. > 300°C. IR (ν/cm⁻¹): 3438, 3347 (NH), strong broad at 2200 (C≡N), 1724 (C=O, coumarin), 1687 (C=O, pyridine). ¹H NMR: δ ppm 2.08 (s, 3H), 6.54 (s, 2H), 7.35-8.05 (m, 8H), 8.41 (s, 1H). MS (EI, m/z): 246 (M⁺, 14.6%). Analysis for C₁₂H₁₃N₂O₁₃: Calcd: C, 53.78; H, 4.80; N, 21.11%. Found: C, 53.65; H, 3.97; N, 19.94%.

6-Amino-4-(3-hydroxy-4-methoxyphenyl)-2-oxo-1-((1-coumarin-3-yl)-ethylidene)-amino)-1,2-dihydropyridine-3,5-dicarbonitrile (9b)

Brown powder, yield = 73%, m.p. > 300°C. IR (ν/cm⁻¹): 3430, 3348, 3237 (NH and OH), strong broad at 2205 (C≡N), 1721 (C=O, coumarin), 1688 (C=O, pyridine). ¹H NMR: δ ppm 2.11 (s, 3H), 3.84 (s, 3H), 6.63 (s, 2H), 6.91-7.65 (m, 7H), 8.47 (s, 1H), 9.61 (s, 1H). MS (EI, m/z): 467 (M⁺, 64.3%). Analysis for C₁₅H₁₄N₂O₇: Calcd: C, 64.24; H, 3.67; N, 14.98%. Found: C, 64.36; H, 3.62; N, 14.88%.

Conclusion

The target of this work involved the preparation and evaluation the anti-cancer activity of some coumarinyl-pyrrole and coumarinyl-pyrimidine scaffolds with the hope of discovering new structure leads serving as anticancer agents. Compounds 7 and 8b proved to be the most important compounds in this study; they displayed very strong activity against the human HepG2 and MCF-7. The other synthesized coumarin scaffolds displayed different degrees of anti-cancer effect, compounds substituted with methoxy and hydroxy groups in benzene ring (derived from isovanillin) showed stronger anticancer activity than their corresponding compounds substituted with nitro group (derived from 4-nitrobenzaldehyde), which displayed moderate and/or weak anti-cancer effect.

References


