Synthesis of 3-(4, 5-dihydro-1-phenyl-5-substituted phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one derivatives and evaluation of their anticancer activity

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Coumarin; Anticancer; Breast cancer cell lines; Renal cancer cell lines

Abstract  A novel series of 3-(4, 5-dihydro-1-phenyl-5-substituted phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one derivatives were synthesized. In the first step salicylaldehyde was reacted with ethylacetooacetate at room temperature by stirring which gives compound (I). Compound (I) when refluxed with substituted benzaldehyde and diethylamine in the presence of n-butanol for 4–5 h gives substituted derivatives (IIa–d). Compounds synthesized in step 2 when refluxed with phenyl hydrazine in the presence of pyridine for 6–7 h gives the title compounds (IIIa–d). All the synthesized compounds were sent to NCI for anticancer activity. Synthesized compounds were tested for anticancer activity against 60 different cell lines. From the data thus obtained it was observed that simple coumarin ring derivatives were more effective in inhibiting the growth of cancerous cell lines, than coumarin-pyrazoline derivatives. Among all the synthesized compounds, irrespective of compounds having simple coumarin ring and coumarin-pyrazoline combination, compounds IIa–c, IIIb and IIIId were potent anticancer agents. Compounds were active for the single dose therapeutic program at the dose of 1.00E-5 molar concentration. The main anti cancer activity is assumed to be due to the presence of the lactone structure in coumarin moiety.

1. Introduction

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. Cancer is thought to be caused by the interaction between genetic susceptibility and environmental toxins. Anticancer drugs available are targeted to damage the aberrantly dividing cell by interrupting the cell division process (Carter et al., 1986). Some of anti cancer agents used include DNA intercalating agents (e.g. adriamycin), DNA cross-linking agents (e.g. cisplatin), topoisomerase inhibitors (e.g. camptothecins), cytoskeleton-disrupting agents (e.g. 
vinblastin) and antimetabolites (e.g., mercaptopurine). These drugs affect “younger” tumors (i.e., more differentiated) more effectively, because they still possess some regulated cell growth. With succeeding generations of tumor cells, differentiation is typically lost, growth becomes less regulated, and tumors become less responsive to most chemotherapeutic agents. Near the center of some solid tumors, cell division has effectively ceased, making them insensitive to chemotherapy.

These anticancer agents though effective, are cytotoxic, and thus exhibit severe side effects, particularly on normal proliferating tissues such as the hematopoietic system (Baronija et al., 2010). Many natural products and other chemicals are put in to reduce the overall side effects of these chemotherapeutic agents. Recently coumarins and its derivatives are extensively studied to treat various types of cancer. Coumarins can be used not only to treat cancer but also to treat the side effects caused by radiotherapy. A recent study investigated the efficacy of coumarin/troxerutine combination therapy for the protection of salivary glands and mucosa in patients undergoing head and neck radiotherapy. The results suggest that coumarin/troxerutine have a favorable effect in the treatment of radiogenic sialadenitis and mucositis (Grotz et al., 2001). Coumarin and coumarin-related compounds have proved for many years to have significant therapeutic potential. They come from a wide variety of natural sources and new coumarin derivatives are being discovered or synthesized on a regular basis. Coumarin is a simple molecule and many of its derivatives have been known for more than a century. However, their vital role in plant and animal biology has not been fully exploited. Coumarins have multiple biological activities including disease prevention, growth modulation and anti oxidant properties. These derivatives have anti-tumor effects and can cause significant changes in the regulation of immune responses, cell growth and differentiation.

In the field of chemotherapy some newer agents are introduced which do not directly interfere with DNA. These include monoclonal antibodies and the new tyrosine kinase inhibitors e.g. imatinib mesylate (Gleevec or Glivec), which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukemia and gastrointestinal stromal tumors). These are examples of targeted therapies. In addition, some drugs that modulate tumor cell behavior without directly attacking those cells may be used. Hormone treatments fall into this category. In case of coumarins as anti cancer agents they act by different mechanisms for different cancerous cell lines (Lacy and O’Kennedy, 2004).

2. Materials and methods

Reaction Scheme: (See Scheme 1).

2.1. Synthesis

2.1.1. General procedure for synthesis of 3-acetyl coumarin (I)

To the cold ethylacetoacetate solution (5 ml, 0.2 M) salicyaldehyde (5 ml, 0.2 M) was added dropwise, few drops of catalyst (diethylamine) were added by continuous and rapid stirring. After 20 min the yellow solid separated was filtered off subsequently washed with ethanol and was recrystallized by ethanol.

2.1.2. General procedure for synthesis of 3-substituted phenyl-5-(3-coumarinyl) propan-1-ones (IIa-d)

A mixture of 3-acetyl coumarin (A, 0.01 M) and different substituted benzaldehydes (0.012 M) were dissolved in n-butanol under heating; (Singh et al., 2011) then 0.3 ml of glacial acetic acid and the same quantity of catalyst (diethylamine) were added. The reaction mixture was refluxed for 4 h and then solvent was removed. The residue was washed with ethanol to remove the remaining solvent. The precipitate was filtered off and crystallized from appropriate solvent.

2.1.3. General procedure for synthesis of 3-(4, 5-dihydro-1-phenyl-5-substituted phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one derivatives (IIIa-d)

3-substituted phenyl-1-(3-coumarinyl) propan-1-ones (B, 0.05 M) were dissolved in pyridine (30 ml), with slight heating then hydrazine hydrate (0.2 M) was added to the mixture which was refluxed for 6 h. On completion of reaction, neutralization was done with 2 N hydrochloric acid. Neutralized reaction mixture was poured onto the crushed ice. The precipitated solid was filtered, dried and recrystallized from appropriate solvent to yield the desired compound (IIIa-d). The compounds were characterized by their physiochemical parameters, IR, 1H-NMR, Mass and elemental analysis data.

All the research chemicals were purchased from sigma–Aldrich (St. Louis, Missouri, USA) and are used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) using silica gel by ascending technique. Melting points of the synthesized compounds were determined by open capillary method and were uncorrected. IR spectra were recorded on Shimadzu FTIR-8400S using KBr pellet technique. The 1H-NMR was recorded on Brucker DRX-300 (300 MHz FT NMR with low and high temperature facility) using CDCl3/DMSO-d6 as solvent. Chemical shifts are reported in δ ppm units with respect to TMS as internal standard. The elemental analysis (C, H, and O) of compounds was performed on Elemental Vario EL III, Carlo Erba 1108 analyzer. Results of elemental analysis were within ±0.5% of the theoretical values. Purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapors as visualizing agents.
2.2. Methodology of the in vitro cancer screen

The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96 well microtiter plates in 100 μL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 °C, 5% CO₂, 95% air and 100% relative humidity for 24 h prior to the addition of experimental drugs (Chaudhary et al., 2011).

After 24 h, two plates of each cell line are fixed *in situ* with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions are added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations (Dudhe et al., 2012).

Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO₂, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the gentle addition of cold TCA. Cells are fixed with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 490 nm. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

\[
\frac{[(Ti - Tz)/(C - Tz)] \times 100}{Ti} \times \text{concentrations for which Ti} \]

Where:

\[
\frac{[(Ti - Tz)/(C - Tz)] \times 100}{Ti} \times \text{concentrations for which Ti} < Tz.
\]

Three dose response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI50) is calculated from [((Ti - Tz)/(C - Tz)] \times 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti – Tz)/Tz] \times 100 = –50. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested (www.dtp.nci.nih.gov).

3. RESULT

All the synthesized compounds were characterized by IR, ¹H NMR, Mass spectroscopy and elemental analysis, with their following spectral data:

3.1. 3-Acetyl coumarin (I)

IR (KBr) Vₘₐₓ: 1741.60 (Lactone of coumarin), 1677.95(C=O), 1454.23(Ar C=O), 757.97(Ar=C–Hdef); ¹H NMR (CDCl₃-d₆ 300 MHz, δ ppm): δ 7.38–7.47 (m, 4H, Ar–H), 8.65 (s, 1H, H of coumarin), 2.5 (s, 3H, –CH₃); EIMS m/z: 189, 171, 135; Anal. Cal. C, 70.21; Found, C, 70.80%.

3.2. 3-[(3-(2, 4-Dichlorophenyl) acryloyl)-2H-chromen-2-one (IIa)

IR (KBr) Vₘₐₓ: 1741.60 (Lactone of coumarin), 1677.95(C=O), 1454.23(Ar C=O), 757.97(Ar=C–Hdef), 1080.06 (Ar =Cl); ¹H NMR (CDCl₃-d₆ 300 MHz, δ ppm): δ 7.22–7.38 (m, 8H, Ar–H), 8.40 (s, 1H, H of coumarin), 4.15 (dd, 1H, trans ethylene); Anal. Cal. C, 62.63; Found, C, 63.12%

3.3. 3-(3-(2, 6-Dichlorophenyl) acryloyl)-2H-chromen-2-one (IIb)

IR (KBr) Vₘₐₓ: 1731.96 (Lactone of coumarin), 1527.52 (Ar–C=Cl), 1608.52 (C=Cstr), 979.77 (Ar C=Cl); ¹H NMR (CDCl₃-d₆ 300 MHz, δ ppm): δ 7.02–7.27 (m, 8H, Ar–H), 8.45 (s, 1H, H of coumarin), 4.15 (dd, 1H, cis ethylene), 3.54 (dd, 1H, trans of ethylene); Anal. Cal. C, 62.63; Found, C, 61.23%.

3.4. 3-(3-(2, 4-Dimethoxyphenyl) acryloyl)-2H-chromen-2-one (IIc)

IR (KBr) Vₘₐₓ: 1722.31 (Lactone of coumarin), 1556.45 (Ar–C=Cl), 1500.95 (C=Cstr), 1384.79 (Ar–OCH₃), 1172.64 (O), 1454.23 (Ar C=O); ¹H NMR (CDCl₃-d₆ 300 MHz, δ ppm): δ 7.02–7.27 (m, 8H, Ar–H), 8.49 (s, 1H, H of coumarin), 4.25 (dd, 1H, H cis of ethylene), 3.50 (dd, 1H, H trans of ethylene), 3.37 (s, 2H, –OCH₃); Anal. Cal. C, 71.42; Found, C, 71.50%.

3.5. 3-(3-(4-Hydroxyphenyl) acryloyl)-2H-chromen-2-one (IId)

IR (KBr) Vₘₐₓ: 1726.95 (Lactone of coumarin), 1550.24 (Ar–C=Cl), 1589.34 (C=Cstr); ¹H NMR (CDCl₃-d₆ 300 MHz, δ ppm): δ 7.02–7.27 (m, 8H, Ar–H), 8.42 (s, 1H, H of coumarin), 4.24 (dd, 1H, H cis of ethylene), 3.50 (dd, 1H, H trans of ethylene), 3.37 (s, 2H, –OCH₃), 3.12 (s, 1H, –OH); Anal. Cal. C, 71.42; Found, C, 71.50%.
Table 1  60 Cell line assay of compound Il in one dose at $10^{-5}$ concentration.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean growth percentage</th>
<th>Range of growth percentage</th>
<th>Most sensitive cell line</th>
<th>Growth of most sensitive cell line percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Il</td>
<td>102.37</td>
<td>-25.60 to 60.55</td>
<td>UO-31</td>
<td>-25.60</td>
</tr>
<tr>
<td>Il</td>
<td>102.37</td>
<td>-19.55 to 60.55</td>
<td>SK-ME 4–5</td>
<td>-19.55</td>
</tr>
<tr>
<td>Il</td>
<td>102.37</td>
<td>-15.50 to 60.55</td>
<td>SNB-75</td>
<td>-15.50</td>
</tr>
<tr>
<td>Il</td>
<td>102.37</td>
<td>-14.8 to 60.55</td>
<td>MDA-MB-231</td>
<td>-14.80</td>
</tr>
</tbody>
</table>

UO-31: Renal cancer lines; SK-ME 4–5: Melanoma cell lines; SNB-75: CNS cancer cell lines; MDA-MB-231: Breast cancer cell lines.

Table 2  60 Cell line assay of compound Iib in one dose at $10^{-5}$ concentration.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean growth percentage</th>
<th>Range of growth percentage</th>
<th>Most sensitive cell line</th>
<th>Growth of most sensitive cell line percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iib</td>
<td>91.78</td>
<td>-42.88 to 73.75</td>
<td>UO-31</td>
<td>-42.88</td>
</tr>
<tr>
<td>Iib</td>
<td>91.78</td>
<td>-35.15 to 73.75</td>
<td>MDA-MB-231</td>
<td>-35.15</td>
</tr>
<tr>
<td>Iib</td>
<td>91.78</td>
<td>-33.68 to 73.75</td>
<td>HOP-62</td>
<td>-33.68</td>
</tr>
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</table>


Table 3  60 Cell line assay of compound Iic in one dose at $10^{-5}$ concentration.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean growth percentage</th>
<th>Range of growth percentage</th>
<th>Most sensitive cell line</th>
<th>Growth of most sensitive cell line percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iic</td>
<td>91.85</td>
<td>-52.42 to 73.84</td>
<td>MDA-MB-468</td>
<td>-52.42</td>
</tr>
<tr>
<td>Iic</td>
<td>91.85</td>
<td>-46.70 to 73.84</td>
<td>NCI-H522</td>
<td>-46.70</td>
</tr>
<tr>
<td>Iic</td>
<td>91.85</td>
<td>-40.04 to 73.84</td>
<td>CAKI-1</td>
<td>-40.04</td>
</tr>
<tr>
<td>Iic</td>
<td>91.85</td>
<td>-31.53 to 73.84</td>
<td>T-47D</td>
<td>-31.53</td>
</tr>
</tbody>
</table>

MDA-MB-468: Breast cancer cell lines; NCI-H522: Non-small cell lung cancer cell lines; CAKI-1: Renal cancer cell lines; T-47D: Breast cancer cell lines.

Table 4  60 Cell line assay of compound IIb in one dose at $10^{-5}$ concentration.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean growth percentage</th>
<th>Range of growth percentage</th>
<th>Most sensitive cell line</th>
<th>Growth of most sensitive cell line percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>98.35</td>
<td>-24.33 to 55.07</td>
<td>NCI-H23</td>
<td>-24.33</td>
</tr>
<tr>
<td>IIb</td>
<td>98.35</td>
<td>-28.42 to 55.07</td>
<td>CAKI-1</td>
<td>-28.42</td>
</tr>
<tr>
<td>IIb</td>
<td>98.35</td>
<td>-29.18 to 55.07</td>
<td>MDA-MB-231/ATCC</td>
<td>-29.18</td>
</tr>
</tbody>
</table>

NCI-H23: Non-small cell lung cancer cell lines; CAKI-1: Renal cancer cell lines; MDA-MB-231/ATCC: Breast cancer cell lines.

Table 5  60 Cell line assay of compound IId in one dose at $10^{-5}$ concentration.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean growth percentage</th>
<th>Range of growth percentage</th>
<th>Most sensitive cell line</th>
<th>Growth of most sensitive cell line percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IId</td>
<td>77.59</td>
<td>-67.37 to 78.46</td>
<td>MDA-MB-231/ATCC</td>
<td>-67.37</td>
</tr>
<tr>
<td>IId</td>
<td>77.59</td>
<td>-65.18 to 78.46</td>
<td>CAKI-1</td>
<td>-65.18</td>
</tr>
<tr>
<td>IId</td>
<td>77.59</td>
<td>-63.77 to 78.46</td>
<td>UO-31</td>
<td>-63.77</td>
</tr>
<tr>
<td>IId</td>
<td>77.59</td>
<td>-67.37 to 78.46</td>
<td>NCI-H522</td>
<td>-67.37</td>
</tr>
</tbody>
</table>

MDA-MB-231/ATCC: Breast cancer cell lines; CAKI-1: Renal cancer cell lines; UO-31: Renal cancer cell lines; NCI-H522: Non-small cell lung cancer.
3.6. 3-(4, 5-Dihydro-5-(2, 4-dichlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (IIIa)

IR (KBr) νmax: 1693.38 (Lactone of coumarin), 1498.59 (Ar C=O), 1548.73 (–C=C), 1598.88 (–C=N), 1072.35 (Ar C–Cl); 1H NMR (CDCl3-d6 300 MHz, δ ppm): 6.43–7.27 (m, 12H, Ar–H), 7.4 (s, 1H, H of coumarin), 4.82 (d, 1H, 5-H of pyrazoline), 3.39 (d, 1H, 4-Htrans of pyrazoline), 4.33 (d, 1H, 4-Hcis of pyrazoline); Anal. Cal. C, 66.22, N, 6.44; Found, C, 66.24, N, 6.42%.

3.7. 3-(4, 5-Dihydro-5-(2, 6-dichlorophenyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (IIIb)

IR (KBr) νmax: 1731.96 (Lactone of coumarin), 1527.52 (Ar C=O), 1660.60 (–C=C), 1588.50 (–C=N), 979.77 (Ar C–Cl); 1H NMR (CDCl3-d6 300 MHz, δ ppm): δ 6.43–7.27 (m, 12H, Ar–H), 7.4 (s, 1H, H of coumarin), 4.98 (d, 1H, 5-H of pyrazoline), 3.79 (d, 1H, 4-Htrans of pyrazoline), 3.84 (d, 1H, 4-Hcis of pyrazoline); Anal. Cal. C, 65.58, N, 6.15%.

Figure 1  Anti cancer spectra of compound IIa.

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3.8. 3-(4,5-Dihydro-5-(2,4-dimethoxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (IIIc)

IR (KBr) $V_{\text{max}}$: 1721.54 (Lactone of coumarin), 1556.45 (Ar C’C), 1606.59 (–C’Cstr), 1596.95 (–C’N), 1172.64 (–OCH3);

$^1$H NMR (CDCl3-d6 300 MHz, $\delta$ ppm): 6.23–7.27 (m, 12H, Ar–H), 7.42 (s, 1H, H of coumarin), 3.73 (s, 6H of –OCH3), 4.88 (d, 1H, 5-H of pyrazoline), 3.29(d, 1H, 4-Htrans of pyrazoline), 3.33 (d, 1H, 4-Heis of pyrazoline); Anal. Cal. C, 73.23, N, 6.57; Found, C, 73.54, N, 6.42%.

3.9. 3-(4,5-Dihydro-5-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-3-yl)-2H-chromen-2-one (IIId)

IR (KBr) $V_{\text{max}}$: 1726.44 (Lactone of coumarin), 1550.15 (Ar C’C), 1624.43 (–C’Cstr), 1590.95 (–C’N); $^1$H NMR

Figure 2  Anti cancer spectra of compound IIb.
(CDCl3-d6 300 MHz, δ ppm): 6.23–7.27 (m, 12H, Ar–H), 7.42 (s, 1H, H of coumarin), 3.03 (s, 1H of –OH), 4.88 (d, 1H, 5-H of pyrazoline), 3.69(d, 1H, 4-Htrans of pyrazoline), 3.83 (d, 1H, 4-Hcis of pyrazoline); Anal. Cal. C, 71.24, N, 6.57; Found, C, 70.62, N, 6.42%.

After synthesis and their characterization compounds were submitted to the NCI 60 cell line screen, which were evaluated initially at a single concentration (10–5 M) in the full NCI 60 cell panel. 60 different human tumor cell lines, representing leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer were utilized in the screening. (See Tables 1–4).

The mean growth, range of growth, and growth relative to most sensitive cell lines are depicted to evaluate the efficacy of the compounds. A broad spectrum of growth inhibitory...
activity against human tumor cell, as well as some distinctive patterns of selectivity has been shown by the tested compounds. Compound IIId of Table 5 was found to be a most active anticancer agent among all other synthesized compounds with minimum mean growth percentage of 77.59.

Maximum inhibition was observed for the cancer cell lines of Renal cancer, Breast cancer and Non-small cell lung cancer. Most inhibited cell lines were Breast cancer (MDA-MB-231/ATCC) and Non-small cell lung cancer (NCI-H522) with growth percentage of 67.37 each as shown in Fig. 5. Other next potent compounds were IIa–c, IIIb with growth percentage of 102.37, 91.78, 91.85 and 98.35 as shown in Figs. 1–4 respectively. (See Graph. 1).

From the results obtained it is evident that the compounds are more effective on Breast cancer cell lines. While comparing the chemical structures of these compounds it shows that...
simple coumarin derivatives (step II) are more effective in inhibiting the growth of cell lines than compared to the coumarin-pyrazoline derivatives.

4. Discussion

Coumarins can be used not only to treat cancer but also to treat the side effects caused by radiotherapy. Here the coumarin derivatives proved to be very effective for specific cancer cell lines. These derivatives are effective for the renal, breast and non-small cell lung cancers.

Coumarins and their derivatives mainly act upon the cell growth cycle of the cancerous cells due to their lactone ring present in them. In every cancerous cell lines they have different actions on the different stages of cell cycle. It has been investigated that coumarins induce G1 arrest of human renal
cancer cell lines, from the results it is evident that hydroxy substitution on coumarin-pyrazoline moiety is proved to be most effective as cytotoxic agents.

The δ-lactone ring of the coumarins is tried to be co-related with the δ-lactone rings of well established Camptothecin esters and sesiquiterpene lactones. Literature shows that these compounds act as anticancer agents by resisting hydrolysis while in circulation, but hydrolyzing their intact lactone ring in the target tissue. Rates of hydrolysis by tumor cells may vary and it is the chief feature which determines the potency of the compounds for particular cancerous cell.

Camptothecins contain a lactone ring that exists in the closed form below pH 7. Above 7, the open (CPT+) and the closed (CPT) form coexist in a 90–10 ratio in human plasma due to the high affinity of human serum albumin (HSA) for CPT+. CPT+ is much less toxic than CPT and it is excreted much faster. Due to variation of rates of hydrolysis Camptothecins were higher by breast cancer and melanoma cells than by colon cancer cells. Apart from hydrolysis, other proposed mechanisms could be that of sesiquiterpene-lactones. SLs react with thiols, such as cysteine residues in the protein, by rapid Michael type of addition. These reactions are mediated chemically by α,β-unsaturated carbonyl system present in the SLs. These studies support the view that SLs inhibit tumor growth by selective alkylation of growth regulatory biological macromolecules such as key enzymes, which controls cell division, thereby inhibiting a variety of cellular functions, which directs the cell into apoptosis. However, other factors, such as lipophilicity, molecular geometry, and chemical environment or the target sulfhydryl may also influence the activity of lactones.

Like these lactone moieties, δ-lactone ring of the coumarins possesses their anti-cancer activity. With various substitutions the hydrolysis of the lactone in the circulation could be prevented and thus this lactone ring by get hydrolyzed by the tumor cells which further may arrest cell division. Here in the present article compound IIId (4-hydroxy substitution) was the most potent anti cancer agent specifically for the Breast cancer (MDA-MB-231/ATCC) and Non-small cell lung cancer (NCI-H522).

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References


