Synthesis And Reactions Of Coumarin Derivatives & Their Biological Activity

Presented By
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Alhamdulilla
Firstly, thanks to Allah S.W.T because giving me success for my final year project.

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With my best wishes

Noura Gamal Doaya
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INTRODUCTION
**Coumarin** (2H-chromen-2-one) is a fragrant organic chemical compound in chemical class the **benzopyrone**, which in its standard state is a colorless crystalline substance. It is a natural substance found in many plants.

**Coumarou** is the a French term for the tonka bean from which a name of coumarin come, one of the sources from which coumarin was first isolated as a natural product in 1820. It has a sweet odor, readily recognised as the scent of new-mown hay, and has been used in perfumes since 1882.

Coumarin is used in certain perfumes and fabric conditioners. Coumarin has been used as an aroma enhancer in pipe tobaccos and certain alcoholic drinks, although in general it is banned as a flavorant food additive, due to concerns regarding its hepatotoxicity in animal models.

![Structure of coumarin](image)

*Figure (1): structure of coumarin.*
Coumarin was **first synthesized** in 1868. It is used in the pharmaceutical industry as a precursor reagent in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to **dicoumarol**, the notable ones being warfarin (brand name **Coumadin**) and some even more potent rodenticides that work by the same anticoagulant mechanism. So-called "coumarins" (modified coumarins) are a type of vitamin K antagonists. Pharmaceutical (modified) coumarins were all developed from the study of sweet clover disease; see warfarin for this history. However, unmodified coumarin itself, as it occurs in plants, has no effect on the vitamin K modifier. Coumarin has clinical medical value by itself, as an edema modifier. Coumarin and other benzopyrones, such as 5,6-benzopyrone, 1,2-benzopyrone, diosmin, and others, are known to stimulate macrophages to degrade extracellular albumin, allowing faster resorption of edematous fluids.[1][2]

Coumarins have an important effects in plant biochemistry and physiology, as they act as antioxidants, enzyme inhibitors, and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection.[3]
Coumarins have long been recognized to possess anti-inflammatory, anti-oxidant, anti-allergic, hepatoprotective, anti-thrombotic, anti-viral and anti-carcinogenic activities.\[4\]

Fig. (2) : Applications of coumarins
PROPERTIES
### Names & Properties

<table>
<thead>
<tr>
<th><strong>IUPAC name</strong></th>
<th>(2H-chromen-2-one)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other names</strong></td>
<td>(1-benzopyran-2-one)</td>
</tr>
<tr>
<td><strong>Chemical formula</strong></td>
<td>C₉H₆O₂</td>
</tr>
<tr>
<td><strong>Molar mass</strong></td>
<td>146.15 g·mol⁻¹</td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>colorless to white crystals</td>
</tr>
<tr>
<td><strong>Odor</strong></td>
<td>pleasant, like vanillabeans</td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>0.935 g/cm³ (20 °C (68 °F))</td>
</tr>
<tr>
<td><strong>Melting point</strong></td>
<td>71 °C (160 °F; 344 K)</td>
</tr>
<tr>
<td><strong>Boiling point</strong></td>
<td>301.71 °C (575.08 °F; 574.86 K)</td>
</tr>
<tr>
<td><strong>Solubility in water</strong></td>
<td>0.17 g/100 mL</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td>very soluble in ether, diethyl ether, chloroform, oil, pyridine, soluble in ethanol.</td>
</tr>
<tr>
<td><strong>log P</strong></td>
<td>1.39</td>
</tr>
<tr>
<td><strong>Vapor pressure</strong></td>
<td>1.3 hPa (106 °C (223 °F))</td>
</tr>
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</table>

### Table (1) : physical properties of coumarins

<table>
<thead>
<tr>
<th><strong>Structure</strong></th>
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</tr>
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<tbody>
<tr>
<td><strong>Crystal structure</strong></td>
<td>Orthorhombic</td>
</tr>
</tbody>
</table>
3- Synthetic Routes for Coumarin

The synthesis of coumarins has been the subject of extensive study over many decades and is usually synthesized by several methods viz the von Pechmann \[6\], Perkin \[7\], Reformatsky \[8\], and Wittig reactions \[9\].

**3.1- Von Pechmann reaction:**

Pechmann reaction is one of the most common procedures for the preparation of coumarin and its derivatives. This method involves the reaction between phenol and \(\beta\)-ketoester in the presence of an acidic catalyst. The reaction is conducted with a strong Brønstedt acid such as methanesulfonic acid or a Lewis acid such as \(\text{AlCl}_3\). The acid catalyses transesterification as well as keto-enol tautomerisation.

![Scheme 1: Pechmann Condensation](image)

scheme (1): pechmann condensation
3.1.1- Reaction mechanism :-

The reaction can also be catalyzed by different Brønsted and Lewis acids *viz.* PPA, ZrCl₄, Yb(OTf)₃, p-TsOH, BiCl₃, and I₂.
3.2 - Perkin reaction:-

In 1868, Perkin \(^{[7]}\) reported the synthesis of coumarin by the reaction of sodium salt of salicylaldehyde with AC\(_2\)O. The Perkin reaction provides a useful method for the synthesis of \(\alpha,\beta\)-unsaturated aromatic acids and involves the condensation of a carboxylic anhydride with an aromatic aldehyde in presence of a weak base such as sodium or potassium acetate or triethylamine.

Coumarin is prepared by converting phenol (1) to salicylaldehyde (2) using Reimer-Tiemann reaction. Then salicylaldehyde undergoes a Perkin reaction with acetic acid and sodium acetate to yield an unsaturated acid (3). Intramolecular esterification of (3) then forms Coumarin (4).

\[
\text{Scheme (3) : perkin reaction}
\]
3.3- Reformatsky Reaction:-

Dittmer et al. have achieved the sodium telluride-triggered cyclization of the bromoacetate of salicylaldehyde to coumarin via modified Reformatsky reaction.[8]

The cyclization proceeds by formation of the phenolate ester enolate, elemental tellurium, and bromide ion. The enolate anion either attacks the ortho carbonyl group leading to cyclization or eliminates a phenolate ion to give a ketene

![Scheme 4: Reformatsky Reaction](image-url)
3.4 - Wittig reaction:

Recently, a novel one-pot synthesis of coumarins via intramolecular Wittig cyclization from the reaction of phenolic compounds containing ortho-carbonyl group and triphenyl(α-carboxymethylene)phosphorane imidazolide was reported by Upadhyay and his group [9].

scheme (5) : wittig reaction
3.5 - Synthesis of coumarins by ring-closing Metathesis:

Investigations into olefin ring-closing metathesis (RCM) have led to a general method for the synthesis of coumarins. Catalysts with higher activity, such as the second-generation ruthenium catalyst, promote the intramolecular reaction between two-electron deficient olefins. This method allows for convenient access to a variety of coumarins substituted at both the 3- and 4-positions, as well as a tetrasubstituted example.

The application of ring-closing metathesis (RCM) in total synthesis has received a great deal of attention, giving synthetic chemists the confidence to subject highly valuable materials to RCM reactions [10].

Applying RCM to the synthesis of novel and important highly functionalized products. Many of these discoveries have been due to the availability of catalysts with varied activities, such as 1[11], 2[12], and 3[13] (Fig. 3). In particular, the development of ruthenium-imidazoylidene catalyst 1, has greatly expanded the substrate range in olefin metathesis reactions.
The application of catalyst 1 in RCM has been demonstrated with several important new results. For example, in macrocyclic RCM where both cis and trans products are formed, greater trans stereoselectivity was observed using catalyst 1 rather than the parent bis-phosphine catalyst 2 [14]. Catalyst 1 provides a synthetically useful 11.5:1 E/Z mixture of olefin isomers in a 14-member lactone, which translates to 250 % enrichment of the trans olefin product as compared to catalyst 2, which provides the product in a 4.5:1 E/Z ratio. This is believed to occur by olefin isomerization to the more thermodynamically favorable trans isomer, which occurs to a greater extent with catalyst 1. In addition, new RCM reaction manifolds have been discovered using catalyst 1. Our group [15] and others [16], have reported the RCM of acrylate esters to form \(\alpha,\beta\)-unsaturated esters and ketones using
catalyst 1 and related derivatives. This unique activity has been expanded to prepare large macrocycles by a ring expansion reaction (Scheme 6).

These reactions proceed via an initial ring-opening of the cyclic olefin, then a cross-metathesis (CM) with one α,β-unsaturated carbonyl olefin, and finally a macrocyclic RCM to generate 18–26-member macrocycles. In general, these reactions proceed in good-to-moderate yields, providing a rapid method to generate macrocyclic carbon structures with trans olefin selectivity.

Scheme (6) : Ring-expansion by sequential ROM / CM / macrocyclic RCM.

While catalyst 1 has been successful in improving substrate scope and stereoselectivity in RCM, we have seen a more dramatic effect within the context of olefin CM. In general, CM has been a less utilized method in
organic synthesis due to low product selectivity and poor olefin stereoselectivity. A wide variety of olefins that do not participate in CM using catalysts 2 and 3 are now viable substrates for highly selective CM reactions that proceed with excellent trans stereoselectivity. Such olefins include α,β-unsaturated carbonyl containing olefins, vinylphosphonate, and vinyl sulfones. In addition, selective CM reactions have been performed between electron-deficient groups in a Heck-type coupling of acrylates and styrenes (Scheme (7)). This was an important discovery because it had been previously proposed that two π-substituted olefins could not participate in selective CM reactions, due to similar electronic properties. Interestingly, there has been no analogous report in the RCM literature that describes a ring-closure between two electron-deficient olefins. This provides a unique opportunity to contribute to the more mature area of RCM, using lessons learned in CM.

Scheme (7): Olefin CM between two electron-deficient olefins.
Coumarins represent an important class of compounds due to their importance in biological systems \(^{[20]}\). There have been a wide variety of noncatalytic methods to synthesize coumarins, such as the Pechmann condensation of \(\alpha,\beta\)-ketoesters \(^{[21]}\). However, this method generally requires strong acids and high reaction temperatures. In addition, there have been several metal-catalyzed approaches to coumarins, including a palladium-catalyzed reaction between phenols and alkynoates \(^{[22]}\). While offering a significantly milder room temperature approach to synthesize these compounds, substitution at the 3-position is not possible due to use of alkyne precursors. There is an example of the synthesis of 3-substituted coumarins by a rhodium-catalyzed carbonylation of alkynyl phenols \(^{[23]}\). While this procedure provides the desired product, it is a minor component with the corresponding 3-benzofuranone. In addition, nickel-catalyzed cross-coupling of coumarin 4-phosphonates been developed as an alternative method to prepare a variety of 4-substituted coumarins \(^{[24]}\).

Therefore, with our previous results in CM between acrylates and styrenes, we were interested in investigating the RCM of similar compounds as a route to substituted coumarins both at the 3- and/or 4-positions (Scheme (8) ). The RCM substrates could be easily prepared by acylation of the corresponding phenol. The required styrenyl phenols may be accessible from a suitable ketone starting material, such as acetophenone. Another advantage of this route is that a variety of acrolyl chlorides can be used to provide substitution at the 3-position, which is not possible using alternative methods. Herein we report the RCM of styrenyl acrylates that provide the coumarin compounds in moderate-to-excellent yield under mild conditions.
Scheme (8) Retrosynthesis of tetrasubstituted coumarins by RCM.

We began our synthesis with the commercially available 2-propenylphenol (4) (Scheme (9)). The acylation step proceeds smoothly with acrolyl chloride to provide 5 in 72% isolated yield. The RCM reactivity of 5 was then explored using catalysts 1 and 2. We were gratified to find that catalyst 1 (3 mol %) provided the coumarin (6) in excellent yield (89%), whereas catalyst 2 (10 mol %) was not able to affect detectable ring-closing. This further illustrated the electron-deficient nature of these substrates, since related chromenes are readily prepared by RCM with catalyst 2 [25]. To investigate the synthesis of more substituted coumarins by RCM, ring-closing precursor compound 8 was efficiently prepared from commercially available 2-hydroxyacetophenone (7) in two steps (Scheme (10)). To afford the ring-closed product, a higher catalyst loading was required (10 mol %), and provided 3,4-dimethylcoumarin (9) in moderate yields.
In addition, the RCM reaction is very clean, allowing for full recovery of unreacted starting material. This reaction is one of the few examples of the formation of a tetrasubstituted olefin by RCM, and is particularly remarkable when one considers the electron-deficient nature of the olefins involved. We also wished to investigate trisubstituted olefins, and the results are summarized in Table (2). RCM provides a unique route to 3-methylcoumarin (10) from
a simple acylation of 4 with methacryloyl chloride, followed by RCM with catalyst 1 in an 88 % isolated yield.

**Table (2) : summary of substituted coumarins by RCM .**

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCM substrate</th>
<th>Catalyst 1</th>
<th>Temp. (°C)</th>
<th>Coumarin product</th>
<th>Isolated yield</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>5 mol %</td>
<td>40</td>
<td><img src="image6.png" alt="Image" /></td>
<td>89 %</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10 mol %</td>
<td>80</td>
<td><img src="image9.png" alt="Image" /></td>
<td>45 %</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>5 mol %</td>
<td>40</td>
<td><img src="image10.png" alt="Image" /></td>
<td>88 %</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>5 mol %</td>
<td>40</td>
<td><img src="image11.png" alt="Image" /></td>
<td>74 %</td>
</tr>
</tbody>
</table>
3.6- A solvent-free synthesis of coumarins using Wells–Dawson heteropolyacid as catalyst:

Substituted coumarins are synthesized from phenols and β-ketoesters by the Pechmann reaction, using a Wells–Dawson heteropolyacid as catalyst by a solvent-free procedure. This one requires low reaction times, 130°C temperature and as little as 1mol% of Wells–Dawson acid, obtaining good to excellent yields of coumarins. The catalyst showed to be reusable with no differences in the yields. The results are compared with those of the reactions performed in toluene solution. The presented synthetic procedure is a convenient, clean and fast alternative for synthesizing 4-substituted coumarins.

Pechmann reaction is the most used method for preparing 4-substituted coumarins since it proceeds from very simple starting materials, phenols and β-ketoesters or α,β-unsaturated carboxylic acids. The reaction involves acidic catalysis, and good yields of coumarins substituted in either or in both rings, can often be obtained. However, rough quantities of mineral acid are usually required in the classical preparations, leading to increase the environmental pollution.

Heteropolyacids are useful solid catalysts because of their superacidic properties.
3.6.1- General procedures for the synthesis of coumarins :-

3.6.1.1- Reaction in toluene solution :-

A mixture of phenol 1 (1mmol) and ethyl acetoacetate/ethyl α-methylacetoacetate 2 (1mmol) dissolved in 3mL toluene, and bulk WD catalyst (1%mmol) (ca. 45mg) was refluxed with stirring for the indicated time (Table (3)), and the mixture was filtered off while hot. The work-up was carried out essentially as stated below, yielding the pure 4-methylcoumarins 3.

![Scheme (11): synthesis of pure 4-methylcoumarin](image)

3.6.1.2- Solvent-free reaction :-

A mixture of phenol 1 (1mmol) and ethyl acetoacetate / ethyl methylacetoacetate 2 (1mmol) was stirred at 130°C in the presence of bulk WD acid (1%mmol) (ca. 45mg) for the indicated time (Table (3)). The reaction mixture was extracted with hot toluene (3·5mL).
The solution was concentrated and the crude product was recrystallized from methanol yielding each of pure 4-methylcoumarins (3).

The procedure described above provides a useful, clean and fast alternative for the preparation of 4-substituted coumarins. For nearly all the substrates, the reaction time is reduced drastically in contrast to classical methods. The time economy, along with the conservation of the catalyst activity and the high recovery of the acid catalyst, play for both low environmental impact and low cost, low formation of wastes, no requiring for the use of adsorbents; and principally, the replacement of corrosive mineral acids.
"Table (3)"

Synthesis of coumarins catalyzed with bulk Wells–Dawson heteropolyacid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol 1</th>
<th>Coumarin 3</th>
<th>Time, h (toluene)</th>
<th>% Yield of 3 (toluene)</th>
<th>Time, h (solvent free)</th>
<th>% Yield of 3 (solvent free)</th>
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<tbody>
<tr>
<td>a</td>
<td></td>
<td></td>
<td>4.5</td>
<td>82</td>
<td>0.7</td>
<td>87</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td></td>
<td>5</td>
<td>83</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td></td>
<td>5</td>
<td>62</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td></td>
<td>4.5</td>
<td>13</td>
<td>1.8</td>
<td>71</td>
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<td></td>
<td></td>
<td>6.5</td>
<td>6</td>
<td>1.5</td>
<td>82</td>
</tr>
<tr>
<td>f</td>
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<td>5</td>
<td>28</td>
<td>1</td>
<td>86</td>
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<tr>
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<td>5</td>
<td>78</td>
<td>0.8</td>
<td>97</td>
</tr>
<tr>
<td>h</td>
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<td>65</td>
<td>1.5</td>
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</tr>
<tr>
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<td>j</td>
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<td></td>
<td>9</td>
<td>84</td>
<td>0.5</td>
<td>87</td>
</tr>
<tr>
<td>Entry</td>
<td>Phenol 1</td>
<td>Coumarin 3</td>
<td>Time, h (toluene)</td>
<td>% Yield of 3 (toluene)</td>
<td>Time, h (solvent free)</td>
<td>% Yield of 3 (solvent free)</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>------------</td>
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<td>------------------------</td>
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<td></td>
<td></td>
<td>1.3</td>
<td>77</td>
</tr>
</tbody>
</table>

"Table (3)"

Synthesis of coumarins catalyzed with bulk Wells–Dawson heteropolyacid
3.7-synthesis of coumarinyl isothiocyanate from amino coumarins:

synthesis of coumarinyl isothiocyanate from amino coumarins using CS2, iodine and pyridine [Scheme (12)]. The attraction of isothiocyanate as synthons is obviously due to its diverse reactions and easy availability. It undergoes nucleophilic addition reactions $^{[28]}$, cycloaddition to unsaturated systems $^{[29]}$, Diels-Alder reaction $^{[30]}$ and reaction with bifunctional compounds to yield heterocyclic derivatives $^{[31]}$.

Isothiocyanates have found wide applications in agrochemical $^{[32]}$ and pharmaceutical industries $^{[33]}$. They have attracted attention as they are potent and selective inhibitors of carcinogenesis in various animal models $^{[34]}$.

Scheme (12) : synthesis of coumarinyl isothiocyanate
3.8 - synthesis of Ethyl coumarin-3-carboxylate :-

Ethyl coumarin-3-carboxylate which known as 3-carboethoxycoumarin and as ethyl 2-oxo-2Hchromene- 3-carboxylate or ethyl 2H-1-benzopyran-3-carboxylate in IUPAC system occupies an important position in the organic synthesis and is used in production of biologically active compounds the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxyl group at the 3-position. \[^{[35]}\]

3.8.1. Knoevenagel Reaction :-

The Knoevenagel condensation of 2-hydroxybenzaldehyde with diethyl malonate was catalyzed with different catalysts to give ethyl coumarin-3-carboxylate \((1)\) scheme (13)

\[
\begin{align*}
\text{O} & + \text{CO}_2\text{Et} \\
\text{OH} & \rightarrow \text{CO}_2\text{Et}
\end{align*}
\]

scheme (13) : Reaction of o-salicylaldehyde with diethyl malonate
The synthesis of ethyl coumarin-3-carboxylate 1 under microwave irradiation conditions was also reported. The title compound was obtained from the reaction of \( o \)-salicylaldehyde and diethyl malonate under microwave irradiation with 86% yield\(^{[36]} \).

The Knoevenagel reaction of \( o \)-salicylaldehyde with ethyl cyanoacetate using sodium bicarbonate followed by hydrolysis of carbonitrile group with hydrochloric acid in ethanol afforded ethyl coumarin-3-carboxylate 1 in 87% yield\(^{[37]} \).

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{Et} \\
\text{OH} & \quad \text{CN} \\
& \quad 1)\text{NaHCO}_3 \\
& \quad 2 \text{HCl} / \text{EtOH} \\
\end{align*}
\]

\[
\begin{align*}
\text{87\%} & \quad \text{1} \\
\end{align*}
\]

Scheme (14) Reaction of \( o \)-salicylaldehyde with ethyl cyanoacetate

3.8.2- Miscellaneous Methods :-

3.8.2.1- Reaction of ketene dithioacetal with salicylaldehyde :-

Ethyl coumarin-3-carboxylate can be also obtained through copper(II)-catalyzed C-C bond forming reactions. The reaction of ketene dithioacetal with salicylaldehyde was catalyzed with copper(II) bromide to afford 1 (scheme (15)).\(^{[38]} \)
Scheme (15): Reaction of ketene dithioacetal with salicylaldehyde.

3.8.2.2 - Cyclization of diethyl ester (2) to ethyl coumarins-3-ester (1):

Tetrabutylammonium fluoride also catalyzes the cyclization of diethyl ester 2 to afford ethyl coumarins-3-ester 1 (scheme (16)).[39]

Scheme (16): Cyclization of diethyl ester (2) to ethyl coumarins-3-ester (1)
3.8.2.3- cyclization of acrylate (3) to ethyl coumarin-3-ester (1)

(E)-Ethyl 2-bromo-3-[2-(methoxymethoxy)phenyl]acrylate 3 was converted into ethyl coumarin-3-carboxylate 1 via two steps. Firstly by treatment with hydrochloric acid in ethanol and secondly cyclization by Pd-catalyzed cross-coupling reaction (scheme (17)).

\[\text{Scheme (17) : Cyclization of acrylate (3) to ethyl coumarin-3-ester (1)}\]
Pechmann reaction of resorcinol (1) and substituted resorcinol with pyrrolidine β-ketoester (2) and indole β-ketoester (4), separately in the presence of conc. H$_2$SO$_4$, gives the corresponding 7-(1,2-dimethylheptyl)-9-hydroxypyrrolo [3,4-c] benzopyran-4-one derivative (3) $^{[41]}$ and 3-hydroxy[1]benzopyrano[4,3-b]indol-6-one (5) as shown in [eqs 1 & 2], respectively. Reaction of 3-aminocoumarin (6) with NaNO$_2$/HCl (diazotization), followed by reduction with Sn(II)Cl, gives coumarin-3-yl hydrazine which, without isolation, reacts with various carbonyl compounds in a Fischer indole synthesis to yield [1] benzopyran [3,4-b]pyrrol-4(3H,4H)-one (7) [eq 3].$^{[42]}$
Scheme (18) : Synthesis of benzopyran [3,4-b]pyrrol-4(3H,4H)-one (7)

3.9.2- Membered Coumarin Heterocycles with One Nitrogen Atom, e.g., Coumarinopyridines, Coumarinoquinolines :-

Coumarins having 3:4-fused six membered heterocycles having one nitrogen atom have been reported. The best method developed reacts 4-(o-methylphenyl)lutidine-3-carboxylic acid sulphate (8) with AlCl\textsubscript{3} in nitrobenzene to give 2,4-dimethyl[1]benzopyrano [3,4-c] pyridine-5-(2H)-one (9) as shown in [Scheme (19)].

The same compound (9) has also been prepared by reaction of 3-acetylcoumarin (10) with cyanoacetamide and acetone in a sealed
tube. Reaction of o-cyano substituted 4-phenyl pyridine derivatives (11), on reflux in 48 % aq. HBr, gives the corresponding coumarinopyridine (9). Reaction of 3-acetyl coumarin (10) with cyanoethylacetate and a keto compound at 165°C gives (9).

Reaction of o-hydroxybenzaldehyde (12) with dicyanomethane and a ketocompound by heating in NH₄OAc, followed by reaction with HCl, gives (9). Reaction of the flavonone derivative (13) with a secondary amine in the presence of acid gives coumarinopyridines (14); the same product is formed on reaction of (13) with cyanoacetamide.

Reaction of (12) with 2-cyanoethyl acetate in NH₄OAc under refluxing conditions gives coumarinopyridine (15). Reaction of 3-coumarino derivative (16) with N-[3-ketobutyl] pyridinium bromide (17) in NH₄OAc/AcOH, followed by oxidation with CrO₃, gives (15).

Reaction of 3-aminocoumarin derivative (18) with unsaturated compounds such as β-ethoxyacrylates (19) [eq 4], propargylic ester (20) [eq 5], and ethyl acetoacetate [eq 6] separately, under thermal conditions, gives coumarinopyridine-4-one derivatives (21), (22) and (23), respectively. 2-Aminocoumarins (18) have been important substrates for preparation of coumarino pyridine derivatives (24) [eq 7] by reaction with glycerol and H₂SO₄.
Scheme (19): synthesis of 2,4-dimethyl[1]benzopyrano [3,4-c] pyridine-5-(2H)-one (9)
Thus, reaction of 4-hydroxycoumarin (25) with anilines (26) and formaldehyde at high temperature (240°C/0.5 torr) gives dihydro coumarinoquinolines (27);[51] when 3-amino-6-methoxypyridine (28)
was used in place of aniline it gives
9-methoxy [1] benzopyran[4,3b][1,5]naphthyridine-6-one (29) \(^{[52]}\)
Reaction of (25) with nitrobenzaldehyde derivatives in the presence of
AcOH/NaOAc and Zn/AcOH gives coumarinoquinolines (30)
[scheme (21) \(^{[53]}\)].
Refluxing 3-(2'-hydroxyaryl)-4-carboxyquinoline (31, \(R=\text{H}\)) in pyridine
hydrochloride gives coumarinoquinolone (32) \(^{[54]}\).

Scheme (21) synthesis of coumarino quinolone (32).
Several coumarino piperidone derivatives (33) have been prepared starting from 3-carboethoxy coumarin (34). Thus, reaction of (34) with several keto compounds (R1CH2COR2) and primary amines (R-NH2) or NH4OAc at 170°C gives coumarinopyridinones (33) [eq 8]. Pechmann condensation of resorcinol derivative (35) with 4-carboethoxy-3-keto piperidine derivative (36) in H2SO4 or POCl3 gives 3:4-fused coumarino piperidines (37) [56]. Mannich reaction of (37) gives aminomethyl coumarino piperdine (38) [57] [eq 9].

![Diagram](image_url)

Scheme (22) : synthesis of aminomethyl coumarino piperdine (38).
3.9.3-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyrazoles:

Reaction of 4-chloro-3-formyl coumarin (39) [eq 10] with phenylhydrazine and phenylsulfoxoy coumarin (40) with diazomethane [eq 11] separately gives the corresponding coumarinopyrazoles (41) and (42), respectively. Coumarins bearing cyano, carboxamido and formyl substituents at C-3 and halo at C-4 are suitable substrates for preparation of coumarinopyrazolines.

Scheme (23): Synthesis of coumarinopyrazolines (41), (42).
3.9.4-Membered Coumarin Heterocycles with Two Nitrogen Atoms, e.g., Pyridazines, Pyrazines :-

Coumarino pyridazines have been prepared by several methods. Reaction of 4-hydroxycoumarino-γ-pyrone (43) with phenyl diazonium salt followed by cleavage with KOH gives 3-phenylpyridazine intermediate (44) which, on reaction with HBr, yields 1-phenyl[1]benzopyrano [4,3-c] pyridazin-5(4H)-one (45) [eq 12]. In another method, reaction of 3-formyl flavone (46) with cyanamide derivatives (47) in the presence of aq.NaOH gives (48). If one follows this by oxidation with CrO₃/pyridine, one obtains benzopyranopyrimidine (49) [eq 13].

Scheme (24) synthesis of benzopyranopyrimidine (49)
Reaction of 3,4,6-trichlorocoumarin (50) with \( \alpha \)-phenylene diamine (51) in the presence of metallic Na, followed by heating in pyridine, gives 2-chloro[1]benzopyrano[3,4-b]quinoxalin-6-one (52) \([\text{eq } 14]\).\(^{62}\)

Reaction of 3-(4-methylphenylsulphonyl)-coumarin (53) with NaN3/DMF at 95 °C gives 1-benzopyrano [3,4-d][1,2,3] triazol-4-(1H)-one (54) \([\text{eq } 15]\).

Scheme (25) : synthesis of 1-benzopyrano [3,4-d][1,2,3] triazol-4-(1H)-one (54).
Reaction of 7-amino-3-phenylcoumarin with NaNO$_2$/H$^+$ gives the corresponding 7-diazo salt (56) which, on coupling with 3-aminocoumarin (55) followed by oxidation with CuSO$_4$, gives fluorescent whitener coumarinotriazole (57) [eq 16].$^{[63]}$

![Diagram of the reaction](image)

Scheme (26) : synthesis of fluorescent whitener coumarinotriazole (57)

### 3.9.5-Membered Coumarin Heterocycles with One Oxygen and One Nitrogen Atom, e.g., Oxazoles, Oxazines :-

Reaction of 3-amino-4-hydroxycoumarin (58) either with acetic anhydride or aliphatic aldehydes in nitrobenzene gives 2-methylbenzopyrano [3,4-d]oxazol-4-one (59) [eq 17].$^{[64]}$
Scheme (27) : synthesis of 2-methylbenzopyrano [3,4-d]oxazol-4-one (59).

Heating of 3-ethoxycarbonyl-4-hydroxycoumarins (60) with phenylhydroxyl amine at 150 °C gives a coumarinisoaxazole, namely, 2-N-phenylbenzo-pyrano [3,4-d] isoxazole-3,4-dione (61) [eq 18]. Refluxing substituted 4-chloro-3-formylcoumarins (62) (R = H) with hydroxylamine in NaOAc gives coumarinoisoxoles (63) [eq 19].[65] Reaction of 3,6-dichlоро-4-(2-hydroxyethylamino)-coumarin (65), prepared from 3,4,6-trichlorocoumarin (50) and ethanolamine, in NaH/THF results in intramolecular cyclization yields 2-chlorobenzopyrano[3,4-b][1,4]oxazin-6-one (66) [eq 20].
Scheme (28)

synthesis of 2-chlorobenzopyran[3,4-b][1,4]oxazin-6-one (66)
3.9.6- Membered Coumarin Heterocycles with One Oxygen and One Sulphur Atom, e.g., Isothiazoles, Thiazoles:

Reaction of 2-methylcoumarino-γ-pyrone (68) with $\text{B}_2\text{S}_3/\text{CHCl}_3$ initially gives (69). Further reaction with $\text{P}_4\text{S}_{10}$/toluene gives 8-methyl-5,10-dioxo-9,9-adithia[9a,Siv]pentaleno[2,1-a]naphthalene-6-one (70); compound (68) itself is obtained from 3-acetyl-4-hydroxocoumain (67) \[66\]. Further hydrolysis of (70) with $\text{H}_2\text{SO}_4$ gives 8-methyl-5,9-dioxo-9a,10-dithia[9a,Siv]pentaleno[2,1-a]naphthalene-6-one (71) as shown in [Scheme (29)].

Scheme (29): Reaction of 2-methylcoumarino-γ-pyrone (68) with $\text{B}_2\text{S}_3/\text{CHCl}_3$. 
Reaction of 4-mercaptocoumarin-3-carboxamide (72) with bromine in EtOAc at reflux gives benzopyrano[3,4-d][1,2]isothiazole-3,4-dione (73)[67] [eq 21]. Electrolysis of 3-thioacetamidocoumarin (74) in CH$_3$CN containing Et$_4$N+ClO$_4^-$ gives 2-methylbenzopyran[3,4-d][1,3]-thiazol-4-one (75) [eq 22].[68]

Scheme (30)

synthesis of 2-methylbenzopyran[3,4-d][1,3]-thiazol-4-one (75)
3.9.7-Membered Coumarin Heterocycles with One Sulphur and One Nitrogen Atom, e.g., Thiazines :-

Coumarinothiazines have been prepared starting from 4-hydroxy- (25) and 3,4-dichlorocoumarin derivatives. Thus, reaction of 3,4,6-trichlorocoumarin (50) with 2-mercaptoethyl alcohol in NaOMe gives 3,6-dichloro-4-(2-mercaptoethylamino)-coumarin (76), which cyclizes in NaH/DMF to give 5-oxo [1] benzopyrano [4,3-b][1,4]thiazine (77) [eq 23]. Heating of 2-mercaptoaniline (78) and 4-hydroxycoumarin (25) in DMSO at 140-145°C gives the coumarinobenzothiazine derivative (79) [eq 24]. Ullmann-Fetvad Jian-type condensation of 4-hydroxycoumarin (25) with 5-aminobenzothiazole (80) and HCHO gives 12-oxo-chromeno [5,3-b] thiazolo [4,5-f] quinoline (81) [eq 24]. 4-Hydroxycoumarin-3-sulphonic acid (82) gives 2-methyl-5-oxo benzopyrano [4,3-e][1,2,4] thiadiazine-4,4(3H)-dioxide (84) on reaction with acetamidine hydrochloride (83) [eq 25].

Scheme (31) : synthesis of Thiazines
4-Reactions of Coumarins (Benzopyran-2-ones)

The chemistry of coumarins has centered on performing reactions at the activated C 3,4-double bond of the α,β-unsaturated lactone. Based on this chemistry, heterocyclic systems have been built. Coumarins with the desired aromatic substitution were built by synthesis starting from appropriate starting material and/or by electrophilic or nucleophilic substitution.

4.1-Fused Coumarins :-

Reaction of 3-acetylcoumarin (1, X1 = COCH3) with phenacyl halide in the presence of NaOEt, according to the procedure of Widman et al. gives 3,4-phenacylidene-3-acetylcoumarin (2, X1 = COCH3) due to insertion of methylene across the C-3,4-double bond; the product is a 3,4-dihydrocoumarin derivative [scheme (32)]

4.2- Cycloaddition Reactions :-

The photodimers of coumarin have been known for nearly 60 years. These have been of interest as furocoumarins, and are known to react with the skin in the presence of light.
They have been used for the treatment of skin depigmentation. Photochemical Reaction \[^{73}^{74}\] across the double bond of coumarins (1), X = H) is reported to give four and six membered 3,4-dihydrocoumarin dimers 3 and 4, respectively \[^{75}^{76}\], due to (2+2) and (2+4) cyclo-addition reactions as shown in [scheme (32)].

**Scheme (32) : synthesis of 3,4-phenacylidene-3-acetylcoumarin (2) & Synthesis of 3,4-dihydrocoumarin dimers (3) and (4)**

4.3 - *Dibenzo-α-pyrone*

The preparation of 3:4-fused 5-member ring coumarins have been accomplished mostly by two protocols. The first and popular one is condensation of the appropriate phenol with cyclopentanone-2-carboxylate under Pechmann condensation reaction conditions as depicted in [scheme (33)].

Phenols (5) \[^{77}\] bearing various substituents (Me, HO, COOH) at C-2 and C-5 were condensed with cyclic β-ketoesters (6) \[^{78}\] (n = 1) by use of POCl\(_3\) or H\(_2\)SO\(_4\) to give 1, 2, 3, 4-tetrahydro cyclopenta [c][2] benzopyran 7 (n = 1) derivatives [scheme (33)].
Pechmann reaction conditions leading to the synthesis of colchicines have been reported.\[^{79}\] In the second approach, straight chain β-ketoesters (8) were condensed with phenols (5), initially resulting in propionic acid residue at C-4; cyclization followed by reduction gives the 5-membered ring containing coumarins (7) \[^{80}\] (n = 1) [scheme (33)].

In an analogous way, the corresponding six membered ring containing coumarins (7) (n = 2) have been prepared by Pechmann condensation. Thus, reaction of various phenols 5 with ethyl cyclohexanone-2-carboxylate (6) under acidic conditions \[^{81}\] gives tetrahydrodibenzo-α-pyrones 7\[^{82}\] (n = 2) [scheme (33)] in yields ranging from 5 to 75%.

![Scheme (33): synthesis of tetrahydrodibenzo-α-pyrones (7)](image)
Condensation of phenols (9) with o-halobenzoic acid (10, \( Y = \text{Br} \)), catalyzed by copper salts, gives fair yields of dibenzo-\(\alpha\)-pyrones (11) \(^{83}\) as shown in [scheme (34)].

Ethanol has been found to be a suitable solvent for the reaction of 2-chloro-, 2-bromo- and 2-bromo-4-methyl benzoic acid \(^{84}\) The yield of (11) decreased in the order 2-bromo->2-chloro-> 2-iodobenzoic acid.\(^{85}\) The condensation reaction of phenols (9) with diazoanthranilic acids \(^{86}\) (10, \( Y = \text{N2+} \)), demethylative cyclization of 2-methoxy-2’carboxybiphenyl (12) \(^{87}\) and oxidative cyclization of 2’-carboxy biphenyl (13) \(^{88}\) gives dibenzo-2-pyrones (11) [scheme (34)]

For oxidative cyclization, chromic acid, \( I_2/\text{CCl}_4 \), and peracetic acid are added to silver salts of biphenyl carboxylic acids.

Oxidation was also effected by use of aroyl peroxides \(^{89}\) cobalt-(II)-catalyst/molecular oxygen and di-tert-butylperoxide \(^{90}\) \( \text{Pb(IV)OAc} \) \(^{91}\) and \( \text{K}_2\text{S}_2\text{O}_8 \) \(^{92}\) [scheme (34)].

The potassium salt of 2’-nitrophenyl-2-carboxylate (13) (\( X=2’-\text{NO2} \)) gives (11) (\( X=1-\text{NO2} \)), due to facile intramolecular displacement \(^{93}\) . The presence of fluorine or bromine in place of the nitro group gives lower yields of (11). Among other methods, dehydrogenation of 3:4-cyclohexenocoumarins (14) by Pd/C and Baeyer-Villiger oxidation of fluorenones gives (11) \(^{94}\)

The reaction of 2-methoxycarbonyl-1,4-benzoquinone (15) with substituted phenols (16) catalyzed by acid in regiospecific way gives substituted dibenzo-\(\alpha\)-pyrones (17) \(^{95}\) Regiospecific cyclization leading to the
formation of 3-chloro-dibenzo-α-pyrone (17) (X = 3-Cl; A, B, C = H) has been reported.

Reaction of 3-methoxycoumarin derivative (18) with primary amine and acetone gives dibenzo-α-pyrone derivative (17). Cycloaddition reaction (2+2) of 3-cyano/ethoxycarbonyl coumarin derivative (19) with diene (20) (xylene/heat) followed by dehydrogenation (Pd/C) gives dibenzo-α-pyrone (11) [scheme (34)]. Oxidation of dibenzopyran derivative (21) with CrO₃ or H₂O₂/AcOH gives (11)[96]

Scheme (34) : synthesis of dibenzo - 2-pyrone (11) &

dibenzo-α-pyrones (17)
cycloaddition of 4-vinyl coumarin derivative (22) with maleic anhydride (23, Y = O) and maleimide (23, Y = N) separately (xylene/heat) gives the coumarin adducts (24) and (25), respectively as shown in [scheme (35)].

Scheme (35): cycloaddition of 4-vinyl coumarin derivative (22)

4.4- Heterocyclic Coumarins

4.4.1- Furanocoumarins

coumarins bearing a heterocyclic system fused at C-3, 4 have been prepared. Heteroatoms such as oxygen, nitrogen, sulphur or combinations thereof have been incorporated into the heterocycle. A five-membered ring containing oxygen atoms can fuse to C-3,4 of coumarin in two possible ways to form furan isomers. Both the isomers can be prepared, starting from 3- or 4-hydroxycoumarin, or directly by decarboxylation of carboxy derivatives as shown in [scheme (36)].
Condensation of two moles of 4-hydroxy coumarin derivative (26) with one mole of α- chloro acetaldehyde diethyl acetal gives 3-(hydroxycoumarin-3-yl)-[3,2-b] dihydrofuran-3-yl) dihydrofuranyl coumarin (27). Two moles of (26) condenses with one mole of oximino acetone and undergoes dehydration (Ac2O/NaOAc) to give furano coumarin derivative (28). A similar reaction of 26 with glycerol gives the hydroxymethyl analog (29).

A-ringfused furan derivative (30) was obtained from 3-propargyl-4-hydroxy coumarin derivative (26, R = CH2CH=CH) due to addition followed by dehydration. Alternatively, the furan derivative (30) was obtained from the 4-O-allyl coumarin derivative (31) by Claisen migration. Reaction of 3-phenylcarbonyl coumarin (26 R=COPh) with acetone, followed by treatment with alkali (NaOH/EtOH) and Cu/quinoline, gives substituted furano coumarin (30) (R1 = COOEt, COOH, H; R2 = C6H5; X = H, Me).

Reaction of the 3-β-hydroxymethyl-4-hydroxycoumarin derivative (32) gives the dihydropyran derivative of coumarin on reaction with HCl/MeOH. Bromination (NBS) followed by elimination of HBr gives the furano coumarin (30) (R1 = R2 = X = H) [scheme (36)].

The same product, α,β-unsaturated pyrone (30), was also obtained by condensation of 4-hydroxy succinic acid in conc. H2SO4. Treatment of the pyrone with NBS gives the corresponding 3-bromo derivative (33). The bromo derivative (33), on treatment with alkali, gives furan-α-carboxylic acid derivative (34) which, on decarboxylation (Cu/quinoline) at 240°C, gives the furano coumarin derivative (30).
Scheme (36): Furanocoumarins

4.4.2- Isocoumestan :-

Pechmann condensation of ethyl 3-oxo-2,3-dihydrobenzofuran-2-carboxylate derivative (35) with resorcinol (36) (X = 3-HO) using 85% aq. H2SO4 gives 9-hydroxybenzofuro[2,3-c][1]benzopyran-6-one (37) (isocoumestan) \(^{106}\) as shown in [scheme 37 ]. 3-Hydroxy coumarin (38), on dehydrogenative coupling with catechol (39) in NaOAc/KIO3 in acetone, gives isocoumestan (40) \(^{107}\) as depicted in [scheme 37 ].
Scheme (37) : synthesis of isocoumestan

4.4.3- Pyracoumarins:

A number of pyracoumarins have been readily synthesized from 4-hydroxycoumarin(41) [scheme (38)]. Michael addition of 4-hydroxycoumarin (41) to α,β-unsaturated ketones or aldehydes (pyridine/reflux) followed by cyclization in R4-OH/HCl gives various hemiacetals of pyracoumarins (42). Many of these compounds have anti-coagulant properties. In a similar way, condensation of 4-hydroxyxoumarin (41) with unsaturated nitriles (43) gives 2-imino-3-ethoxy carbonyl pyrazacoumarins (44). Reaction of (41) with cinnamyl bromide (45) gives 3-alkylated coumarin derivative which, on reaction with bromine in CHCl3, yields 2-phenyl-3-bromo pyrazacoumpyran (46). Warfarin (47) on reflux in Ac2O/HClO4 gives the corresponding acetal (48) (20%) and pyran (49) (50%).
Scheme (38): synthesis of Pyranocoumarins
4.4.4- Chromenocoumarins (Chromans):-

Chromenocoumarins have been prepared by 1) Pechmann condensation, 2) Michael addition of coumarins to α,β-unsaturated ketones, 3) condensation of Mannich bases, and 4) condensation reactions of aromatic aldehydes as shown in [scheme (39)].

Thus, Pechmann reaction of resorcinol with 3-hydroxy-6,7-dimethoxy-A3-chromene-4-carboxylate in 85% H2SO4 gives chromenocoumarin.[112] In the second method, Michael addition of 4-hydroxycoumarin (41) to α,β-unsaturated ketones (50) in pyridine gives 6-oxo-7-acetonylbenzopyran-[4,3-b][1]benzopyran (51b) [113]. In the third method, reaction of 4-hydroxycoumarin (41) with HCHO/PhCH2NH2 gives Mannich base (52) which, on heating with phenol, gives coumarinochroman (53).[114]

In the fourth method, reaction of (41) with aldehydes such as citral, citronellal (54) in pyridine, gives chromenocoumarin (55). Reaction of two moles of (41) with glyceraldehydes (56) by refluxing in dioxane gives chromenocoumarin (57) [scheme (39)], and on reaction with o-chlorobenzaldehyde derivative (58), by first refluxing in ethanol and then heating to 200°C in xylene, gives chromenocoumarin (59).[115]

Under similar reaction conditions, heterocyclic chromenocoumarins containing nitrogen (60) have also been prepared85-85 by reaction of (41) with 2-pyridine-2-aldehyde derivatives (61). Reaction of (41) with o-
halophenol (62) in pyridine followed by reflux in MeOH/HCl gives chromenocoumarin (63) in good yield.

The same product has also been prepared by reaction of (41) (HCl and POCl3) with hydroxyl α-phenyl ethyl alcohol 64 as shown in scheme (39).
**4.4.5- Coumarino-α-pyrones :-**

Coumarino-α-pyrones have been synthesized by: 1) condensation of o-hydroxyphenylacetic acid with benzylpyruvic acid, 2) condensation of 4-hydroxycoumarin with either benzylidene malononitrile or malonic acid under Pechmann conditions, 3) cyclisation of 4-hydroxycoumarin-3-propionic acid, and 4) by acylation of 3-acyl-4-hydroxycoumarin as shown in [scheme (40)].

Condensation of 4-hydroxycoumarin (41) with benzylidene malononitrile (65) in pyridine and AcOH/HCl/Ac₂O gives 4-phenylcoumarino-3,4-dihydro-α-pyrone (66).[117]

Pechmann condensation of (41) with ethylacetoacetate (R = H) gives coumarino-α-pyrene (67),[118] in the presence of condensing agents such as AlCl₃, 80% H₂SO₄ and POCl₃. Reaction of (41) with diaryl malonates (68) and AlCl₃, or malic acid (69) and cyanoacetic acid (70)[119] catalyzed by acid, gives coumarino-α-pyrones (71) and (72), respectively. Reaction of 4-hydroxy coumarin(41) with α,β-unsaturated esters (73), catalyzed by piperidine and acetic acid, gives (74).[120] Reaction of 4-hydroxy coumarin (41) with triethyl orthoformate in the presence of aniline gives (75).[121] Reaction of (41) with 2-acetyl diethyl malonate (76) in AlCl₃/C₆H₅NO₂ at 110°C gives (77). Chlorine containing derivatives of coumarino-α-pyrones (78, R₁ = R₂ = Cl) were prepared by reaction of (41) with hexachloroethylene (79) in AlCl₃/CS₂.[122] Several 3-cyano-3-carboethoxy and 3-carbamido coumarino-α-pyrones (80) were prepared by reaction of (41) with the corresponding malonic acid derivatives (81) (X₁-CH₂-X₂) in pyridine at room temperature.[123]
Scheme (40) : Coumarino-α-pyrones
4.4.6- Coumarino-γ-pyrones :

The synthesis of coumarino-γ-pyrones (82), (83) have been described by:
1) Michael addition of 4-hydroxy-coumarin (41) to α,β-unsaturated carboxylic acids (84) or acid chlorides followed by cyclization in PPA to give dihydro-γ-pyrones (82) \[^{124}\] as depicted in [Scheme (41) ],
2) reaction of 2-acetyl coumarins (85) with acetic anhydride in the presence of NaOAc or KOAc,\[^{125}\] and 3) by reaction of (41) with ethylacetooacetate/CF3COOH.

Reaction of (41) with isoxazole (86) by refluxing in pyridine/CuCl\(_2\) gives coumarino-γ-pyrone (87), containing the isoxazole ring.\[^{126}\]

![Scheme VIII](image-url)

Scheme (41) : synthesis of coumarino-γ-pyrones
4.4.7- Coumarino Coumarins :-

Reaction of 3-hydroxyflavone with Ac2O/NaOAc, followed by photolysis, gives bis-3,3’-oxaaindanone derivative (88) which, on oxidation with KMnO4, gives coumarino coumarins (89)\[^{127}\] [scheme (42)]. Alternatively, demethylative ring closure of 3-(2’methoxyphenyl)-4-ethoxycarbonyl coumarins (90) in pyridine/HCl also gives (88).\[^{128}\] A new synthesis of (88) has been described from 2, 2’-dimethoxydiphenyl succinonitrile (91) by reaction with pyridine hydrochloride at 210°C. A simple 3,3’-bis-oxaaindnone (92), on reduction with 10 % NaOH, gives (88). Condensation reaction of 4-hydroxycoumarin (41) with o-halobenzoic acid derivatives (93) in alkaline aq.CuSO\(_4\) gives (89).\[^{129}\]

![Scheme (42): synthesis of Coumarino Coumarin](image)

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4.4.8- Chromones :-

Condensation of resorcinol 5 with coumarin 3-carboxylic acid chloride (94) under Friedel-Craft’s conditions (AlCl₃/C₆H₅-NO₂), followed by oxidation with Pb(IV)OAc/AcOH, gives chromone (95)[130] as shown in [scheme 43]. Coumarino benzopyrans (96) on oxidation with (CrO₃/AcOH) also gives (95)[131]

Scheme (43) : synthesis of chromone

Oxidation of active methylene containing rotenone (97) by CrO₃/AcOH gives the oxidized product of rotenone (98). Acid catalyzed reaction of isoflavone (99) with HBr/AcOH gives benzopyrano-[3,4-b] benzopyran-6,12-dione (100).

Scheme (44) : synthesis of oxidized product of rotenone & benzopyrano-[3,4-b] benzopyran-6,12-dione
4.5-Coumarin as precursor in Organic transformations

4.5.1- Bargellini condensation :-

Venkateswaran and co-workers \cite{132} have described a one-step conversion of coumarins to usefully functionalized diacids employing the Bargellini condensation.

diacid was transformed in a few steps to high yielding marine sesquiterpene Helianane underscoring the importance of this protocol [Scheme (45)].

\[
\begin{align*}
\text{R}^2 \quad \text{R}^1 \\
\text{R}^3 \quad \text{R}^3 \quad \text{R}^3 \\
\text{i. CHCl}_3, \text{NAOH acetone} \\
\text{ii. H}^+ \\
\end{align*}
\]

Scheme (45) : synthesis of functionalized diacids by Bargellini condensation

4.5.2- A direct arylation of 4-hydroxycoumarins by photo induced reaction with aryl Halides :-

A direct arylation of 4-hydroxycoumarins by photo induced reaction with aryl halides was reported by Baumgartner21 et al.\cite{133} in good yields (>60%) [Scheme (46)].
However, the reaction of 4-hydroxycoumarins with o-dihalobenzenes leads to the synthesis of ring closure products which bear a tetracyclic aromatic-condensed ring system with an overall yield of 45% [Scheme (46)].

**Scheme (46)**: direct arylation of 4-hydroxycoumarins with aryl halides

4.5.3-direct arylation of 4-hydroxycoumarins with arylboronic acids:

A method for direct arylation of 4-hydroxycoumarins with arylboronic acids via C–OH bond activation catalyzed by PdCl₂ operable under mild conditions was reported by Wu et al.⁻¹⁴³, to give rise the corresponding 4-arylcoumarins in good to excellent yields [Scheme (48)].
direct arylation of 4-hydroxycoumarins with arylboronic acids

**4.5.4- synthesis of functionalized angularly-fused Dihydrofurocoumarins**

An efficient and straightforward synthesis of functionalized angularly-fused dihydrofurocoumarins by an efficient multi-component domino process of aromatic aldehydes, 4-hydroxycoumarin and α-chloroketones in refluxing n-propanol is described by Altieri et al\[35\]. The products were formed with high diastereoselectivities [Scheme (49)].
The synthesis of 2-benzazepine derivatives was reported by Prasad et al.\textsuperscript{136} from 4-chloro-3-formyl coumarin and benzyl amine under catalyst-free conditions in aqueous medium [Scheme (50)].

"Scheme (50)"

synthesis of 2-benzazepine derivatives
4.5.6- enantioselective Michael reaction :-

Yang co-workers\textsuperscript{[137]} reported enantioselective Michael reaction of 4-hydrocoumarin, using LiClO\textsubscript{4}/DPEN as a catalyst (up to 94 \% ee) [Scheme (51)].

"Scheme ( 51 )"

enantioselective Michael reaction
4.5.7-base-mediated cyclocondensation of 1,3-dicarbonyl to provided various chromeno:

Langer and his group\textsuperscript{[138]} carried out the base-mediated cyclocondensation of 1,3-dicarbonyl compounds with 4-chloro-3-nitrocoumarin, which provided a convenient approach to various chromeno[3,4-b]pyrrol-4(3\textit{H})-ones [Scheme (52)].

"Scheme (52)"

synthesis of chromeno[3,4-b]pyrrol-4(3\textit{H})-ones
Biological activity
5.1-Introduction :-

Coumarin (1,2-Benzopyrone or 2H-1-benzopyran-2-one, or phenylpropanoids, (1) and its derivatives (coumarins) are widely distributed throughout nature and many exhibit useful and diverse biological activities \(^{[139,140]}\). Coumarins occur as secondary metabolites in the seeds, roots and leaves of many plant species, notably in high concentration in the tonka bean and thus the name comes from a French word, coumarou, for the tonka bean. Their function is far from clear, although suggestions include plant growth regulations, fungistasis, bacteriostasis and, even, waste products \(^{[141]}\). Some naturally occurring coumarin derivatives include warfarin (2), umbelliferone (7-hydroxycoumarin, (3), aesculetin (6,7dihydroxycoumarin, (4), herniarin (7-methoxycoumarin, (5), psoralen (6) and imperatorin (7). Now the diversity of coumarin derivatives, both natural and synthetic, has grown and are thus divided into several subclasses. Most reviews classify coumarins according to whether particular compounds are simple coumarins (e.g. coumarin, 1 and limettin, (8) , linear furanocoumarins (e.g. imperatorin,(7) and isopimpinellin, (9) , angular furanocoumarins (e.g. angelicin, (10), linear pyranocoumarins (e.g. xanthyletin, (11) or angular pyranocoumarins (e.g. seselin, (12) \(^{[142]}\). Murray et al. \(^{[143]}\), however, used a biogenetic approach
based upon the number of nuclear oxygen atoms in classifying coumarin-containing compounds

Coumarin derivatives have been found to have numerous therapeutic applications including photochemotherapy, antitumor and anti-HIV therapy\[144,145\], and as central nervous system (CNS) stimulants\[146\], antibacterials\[147,148\] antiinflammatory\[149\], anti-coagulants\[150\] and dyes\[151\]. In addition, coumarins are known to be lipid lowering agents with moderate triglyceride lowering activity\[152\]. Furthermore, hydroxycoumarins, powerful chainbreaking antioxidants and can prevent free radical injury by scavenging reactive oxygen species\[153\]. Some of the coumarin derivatives formerly used as fixative and flavoring agents, are now regulated as food adulterants by the Food and Drug Administration (FDA) in the United States due to their adverse effects such as mild nausea, diarrhea, and hepatotoxicity when used in certain amounts\[154-157\].

Although currently marketed in several European countries, coumarin type drugs such as coumarin (1), used for the treatment of lymphoedema, has not been approved for therapeutic purposes in the United States, due to their hepatotoxicity. However, recent discovery of coumarins having weak estrogenic activity resulted in the use of such derivatives as therapeutic agents in preventing the emergence of menopause related diseases, such as osteoporosis, increased risk for cardiovascular event / disease and cognitive deficiencies\[158\].

The pattern of substitutions on the basic chemical structure is said to influence both the coumarin’s pharmacological and biochemical properties, including the therapeutic applications, and can beneficially affect toxicity (Table 4)\[159-161\]. For example
(1)- introduction of a **methoxy group** at the 7-position and a **3-methyl-2-buteryl group** at the 8-position of osthole (13) led to a strong reduction of plasma alkaline transferase (ALT) level in hepatitis and inhibition of caspase-3 activation [162].

(2)- Some coumarins display **cytostatic** properties (**growth-inhibitory**) while others have cytotoxic activities [163]. For example, **coumarin** and its active metabolite, **7-hydroxycoumarin**, demonstrated growth-inhibitory cytostatic activity in human cancer cell lines, such as A549 (lung), ACHN (renal), H727 (lung), MCF-7 (breast) and HL-60 (leukemia), and have also been reported to demonstrate activity against prostate cancer, malignant melanoma, and metastatic renal cell carcinoma in clinical trials [164-167].

(3)- Furthermore, the substituted **benzopyranobenzothiazinones** expressed estrogenic activity on MCF-7 breast carcinoma cells [168]. It has been demonstrated that the incorporation of a catechol to the basic structure of coumarin would increase cytotoxic activity in tumor cell lines [169].

(4)- Naturally occurring coumarins (NOCs), (e.g. 3 and 8) induce mouse skin tumor initiation in a well-established model of multistage carcinogenesis [170-174]

Among the diverse biological activities of coumarins, the most intriguing is the notable effect of some of the coumarins against breast cancer. Studies have shown that compound 3 as well as 4-hydroxycoumarin inhibited cell proliferation in a gastric carcinoma cell line [175]. An in vitro proliferation assay of the mechanism of action of coumarins on the growth and metabolism of human tumor cells e.g. MCF-7 and A549 confirmed that coumarin itself is not responsible for the observed in vivo effects, but it is a prodrug of other active metabolites [176]. Previous studies have indicated
that the ortho-dihydroxycoumarins (e.g. 4) or meta-dihydroxycoumarins possessed more potent cytotoxicity in human tumor cell lines than any of the mono-hydroxycoumarins [177,178].

Of particular interest in breast cancer chemotherapy, some coumarins and their active metabolite 7-hydroxycoumarin analogs have shown sulfatase and aromatase inhibitory activities. Coumarin based selective estrogen receptor modulators (SERMs) and coumarin-estrogen conjugates have also been described as potential antibreast cancer agents. Since breast cancer is the second leading cause of death in American women behind lung cancer, there is a strong impetus to identify potential new drug treatments for breast cancer. Therefore, the objective of this review is to focus on important coumarin analogs with antibreast cancer activities, highlight their mechanisms of action and structure-activity relationships on selected receptors in breast tissues, and the different methods that have been applied in the construction of these pharmacologically important coumarin analogs.
"Fig (4)"

structure of some naturally occurring coumarins.
Breast cancer is a major cause of mortality in western countries and it has been reported that about one-third of postmenopausal breast cancer patients have hormone-dependent tumors involving the stimulation of estrogen receptor \[^{[179]}\]. Treatment as well as prevention has been the focus of much laboratory work and clinical trials over the past 30 years. Clinical studies focusing on the use of therapeutic agents that prevent the synthesis and action of estrogens (ER antagonists) are known to be very successful in the treatment of breast cancer \[^{[180]}\]. The current strategy thus involves the development of ER antagonists as a new approach for the treatment of postmenopausal women with hormone-dependent breast tumors. The high levels of estrogen as a result of its in situ synthesis are associated with the growth of tumors in endocrine-dependent tissues. Estrogens are formed exclusively in peripheral tissues, and there are two pathways associated with their synthesis in such tissues, the aromatase and sulfatase pathways (Fig. 5). The aromatase pathway involves the conversion of androgen precursor, androstenedione, secreted mainly by the adrenal cortex, to estrone by the aromatase (AR) enzyme complex, while the estrone sulfatase pathways (E1-STS) involves the conversion of estrone formed via the aromatase route to estrone sulfate (E1S) by the sulfotransferase enzymes \[^{[182]}\]. In the breast tumors, activity of the latter enzyme is higher than that of the former, resulting in poor prognosis \[^{[183{--}186]}\]. The E1-STS pathway is considered the major source leading to estrogen formation, causing low response rate in ER+ breast tumor patients to highly potent AR inhibitor \[^{[187{--}190]}\]. Furthermore, studies have shown that endocrine therapy
Involving the inhibition of enzymes within the steroid biosynthetic cascade may be one route to controlling the disease. This approach has led to the development of novel coumarins as STS \textsuperscript{191} as well as AR inhibitors \textsuperscript{192}.

**Fig (5)**: Estrogenic steroid origins showing the sites of action of coumarins AR, aromatase; ST, sulfotransferase; STS, sulfatase; 17(β-HSD, 17β- hydroxysteroid dehydrogenase; ER, estrogen receptor)

- 96 -
5.2.1-Sulfatase Inhibitor:

As illustrated in Fig. (5), the cleavage of sulfated steroid hormone precursors, e.g. estrone sulfate, to the active hormones by STS represents the first step in the local production of estrogen and androgens. Therefore, the inhibition of this enzyme (STS), which should decrease the biosynthesis of active hormones, has been a new therapeutic option in the treatment for hormone-dependent diseases\textsuperscript{[193–196]} such as breast, endometrial and prostate cancers, acne and androgenic alopecia\textsuperscript{[191, 197–199]}. Since STS catalyzes the hydrolysis of sulfate monoester bonds in a range of physiological substrates, the incorporation of a sulfamate ester group linked to an aryl ring was considered to be key strategy in the development of potent STS inhibitors\textsuperscript{[180, 200–203]}. Furthermore, attempt to identify nonsteroidal STS inhibitors led to the development of various bicyclic and tricyclic coumarin sulfamates, which are active both in vitro and in vivo (Fig. 6)\textsuperscript{[204–208]}. A number of potential STS inhibitors are still in preclinical phases of development with only 667 COUMATE (30)\textsuperscript{[209]} set to enter clinical trials for the treatment of hormone-dependent breast cancer in postmenopausal women. Chemically, bicyclic and tricyclic COUMATES (23–37) and their close relatives the 676 OXEPINs (e.g. 38) are aryl sulfamates (Ar-SO2NH2), which are irreversible inhibitors of STS. The crystal structures of the soluble enzymes arylsulfatase A (ASA) and arylsulfatase B (ASB)\textsuperscript{[210, 211]} have provided an insight in the mechanism through which sulfamate group irreversibly inactivates steroid STS. The mechanisms for irreversibly inhibiting STS activity by COUMATES and its congeners (Fig. 7-9)
involve: 1) the L-Cα-formylglycine (FGly), 2) the aldehyde hydrate (gem-diol residue), and 3) random specific or nonspecific sulfamoylation of amino acid residues in the active site \[^{200, 201, 212-216}\]. Random specific or nonspecific sulfamoylation is proposed to occur via two mechanisms – a direct nucleophilic attack by the amino acid residue at the sulfur atom of, for example, compound 30 and elimination of sulfamic acid by an E1cB mechanism, assisted by the extended conjugation present in the coumarin ring \[^{201,217}\].

Structure-activity relationship (SAR) studies of the “locking effect” of the lactone ring structure of the COU-MATE by Ahmed et al. confirmed that conformational restriction of the conjugated C=C bond plays an important role in the potency inhibitory activity displayed by coumarin-based compounds, in addition to the overall size of the inhibitors \[^{218}\]. The pKa value of compound 30 is 9.1 in methanol/water (1:1), making it possible to exist in monoanionic form under physiological condition \[^{201}\].

Compound 30 (Fig. 6) is a nonsteroidal irreversible STS inhibitor and is the most potent of a series of tricyclic COUMATE developed with annulated carbocyclic ring systems at positions 3 and 4 \[^{179, 199, 206}\] with a very acceptable toxicological profile. It has an equipotent in vivo STS activity compared to estrone-3-O-sulfamate (EMATE), a potent, active sitedirected, irreversible steroidal STS inhibitor \[^{219}\]. Moreover, Compound 30 is reported to be active both in vitro and in vivo \[^{205}\] in causing significant regression of E1S-stimulated tumor growth without any sign for estrogenic effect \[^{220}\].

SAR studies involving bicyclic COUMATES revealed that compound 25 (Fig. 6) displays stronger binding affinity for the enzyme active site via a hydrophobic interaction provided by the methyl groups at the 3- and 4-
positions, thereby mimicking the A/B ring of EMATE. Bilban et al. [221] demonstrated that the oxygen functionality substitution at position 7 of the coumarin core structure also mimics the A/B ring of EMATE. Previous computer-modelling study has shown that the seven-membered ring (third ring) of COUMATE (30) could not be described as closely mimicking the C/D ring regions of EMATE, attributed to its chair conformation form which is similar to the cycloheptene ring structure [201, 222]. However, recent finding indicated that the third ring appears to be predominately in the boat conformation rather than previously proposed chair conformation based on temperature factors (B-factors) and electron density map results [217]. With the advent of this new finding regarding the conformation of the 7-membered ring on compound 30 it can now be explained that its higher potency (IC50 value of 8 nM and Ki value of 40 nM) than EMATE (IC50 = 25 nM and Ki = 670 nM) is attributed to the tendency to mimic the steroidal CD-ring; perhaps, better hydrophobic interactions due to favorable binding to the active site of the enzyme are in play [199, 223, 224].

**Benzocoumarin sulfamates** (e.g. 39 and 40), another group of aryl sulfamates closely related to compound 30, mimics the ABC-ring of the steroidal skeleton. Although less active than EMATE, these sulfamates show high inhibitory potency due to strong binding of the benzocoumarin core structure to the enzyme. Removal or disruption of the coumarin ring conjugation results in lower potency [180, 207, 225] due to the resulting higher pKa value for the parent phenol. The extended conjugation present in the coumarin ring structure assists in the S-O-Ar bond breakage during E1-STS catalyzed sulfamoylation by improving the leaving ability of the coumarin compound as a result of lower pKa value of the phenol [201]. On the contrary, an extension of the coumarin conjugation core structure and the
relocation of the sulfamate group to the 6-position of the ring resulted in lower potency exhibited by the COUMATE analogs \(^{180}\).

"Fig (6)"

Structures of coumarin sulfamates and tricyclic coumarin sulfamates
"Fig (7)"

The proposed mechanism of STS inhibition by (30) involving Fgly in the enzyme active site.

"Fig (8)"

Proposed mechanism of STS inhibition by (30) involving the aldehyde hydrate in the enzyme active site.
"Fig (9)"

The proposed random specific or non-specific sulfamoylation by (30).

Path A: a direct nucleophilic attack by the amino acid residue at the sulfur atom. Path B: elimination of sulfamic acid by an E1cB mechanism.
5.2.2-Aromatase Inhibitor :-

Aromatase inhibitors (AIs) include drugs that are currently used for the treatment of hormone-dependent breast cancer, which involves blocking the estrogen action on tumor cells by preventing the biosynthesis of estrogen \[^{226}\]. AI prevents breast cancer via reduction of cell proliferation, which involves reduction of estrogen level and thus prevention of the formation of genotoxic metabolites of estrogen. The genotoxic estrogen metabolites include 1) catechol estrogens, which bind covalently to DNA and induce mutations that initiate cancer; 2) 2-hydroxyl-estradiol, which forms stable DNA adduct; and 3) 4-hydroxyestradiol, which is a potential carcinogenic metabolite forming depurinating estrogen-DNA adducts with guanine base that are unstable and are rapidly lost from the DNA \[^{227-229}\]. Clinical trial results have shown AIs to be of superior efficacy to tamoxifen as antiestrogenic compounds with more favorable toxicity profiles \[^{230-232}\]. In postmenopausal women, AIs have the potential to suppress circulating estrogen levels by approximately >96.7–98.9 % and also abrogate autocrine and paracrine estrogen production by peri-tumoral stromal cells located in both primary and metastatic sites of the tumor \[^{233-239}\]. The FDA has approved a number of AIs, e.g., anastrozole (Arimidex), exemestana (Femara) and letrozole (Aromasin), as first-line agents for the treatment of postmenopausal women with hormone receptor positive breast cancer \[^{240-244}\]. In postmenopausal women, clinical results have shown that AIs used only as monotherapy are very effective in treating estrogen-dependent and aromatase-mediated diseases including breast cancer \[^{245}\]. However, in premenopausal women there is an incomplete blockade of estrogen synthesis resulting in a reflux rise in gonadotrophin level, which in turn can stimulate ovarian aromatase and overcome the estrogen suppression \[^{246}\].
As discussed in previous section, several coumarin derivatives have been reported to be steroid STS inhibitors and evaluated for breast cancer therapy \cite{191, 247}; however, clear evidence of AIs as antibreast cancer agent has not been demonstrated yet. Studies have shown benzopyranone substrates such as 4-benzyl-3-(4’-chlorophenyl)-7-methoxy-coumarin (41) to be a more potent competitive AI than several known AIs such as aminoglutethimide with respect to the androgen substrate. The specific interaction of compound 41 with the AR shows a further reduction by several mutations in binding at the active site region of AR. In addition, compound 41 suppressed the proliferation of AR and ER positive MCF-7 breast cancer cells. It is neither cytotoxic at concentrations up to 40 µM nor an inhibitor of steroid 5α-reductase and also is not a ligand of ERs, ERα and ERβ, or androgen receptor. Thus demonstrating that coumarin derivatives, which are potent inhibitors of aromatase, may not be cytotoxic yet can be useful in the suppression of AR and ER-positive breast tumors.

The SAR studies of (41) revealed that coumarin rings mimic the A and B rings, while the 3(4-chlorophenyl) group 2670 mimics the D ring of the androgen (42) \cite{192}. The methyl group at the C-19 of the androgen substrate, where the first and second hydroxylation reactions take place, points toward the heme group of AR \cite{248}. The spatial orientation of the 4-benzyl group of the coumarin showed that it is aligned very closely to the methyl group at the C-19 position of the substrate. This behavior is attributed to the bending of the benzyl group (through the methylene group), resulting in overlay of the ring on top of the 3-(4-chlorophenyl) group. Furthermore, the 7-methoxyl group of coumarin (41) also aligns very closely with the C-3 keto oxygen of the substrate. These groups- 3-(4chlorophenyl), 7-methoxyl and 4-benzyl- share the same
physicochemical feature that is being hydrogen bond donor groups and are superimposable. However, result has demonstrated that the replacement of the 7-methoxyl group with 7-hydroxyl group on the coumarin significantly decreased the inhibitory activity against AR. A recent study has demonstrated that the presence of an electron-withdrawing group in the phenyl group, e.g. 3(4-chlorophenyl) group, increase activity as a result of such group alignment that mimics the C-17 keto oxygen of estrone \[^{192}\]. Thus it is strongly suggested that 7-methoxyl, 3-(4chlorophenyl) and 4-benzyl functional groups are very critical for the anti-AR activity of the coumarin derivative \[^{192, 249, 250}\]. For example, the IC\(_{50}\) value of 4-benzyl-3-(4chlorophenyl)-7-methoxycoumarin is 80 nM and the replacements of any of the three mentioned functional groups resulted to reduction in potency, e.g. 4-benzyl-3-(4’chlorophenyl)-7-hydroxycoumarin (IC\(_{50}\) 300 nM). A proposed pharmacopore hypothesis indicated that the methoxy group might act as hydrogen bonding acceptor depending on its spatial position relative to the nitrogen atom coordinating the iron (II) \[^{250}\], although there are varieties of possible binding modes, which may differ from those of the unsubstituted coumarin derivatives. The carbonyl group of the coumarin lactone ring is another structural determinant for the observed coumarins’ AR inhibitory activity. Also, a favorable interaction at the 7-position of the coumarin ring is due to the formation of a hydrogen bond by the 7-oxygen atom and the lipophilic or \(\pi-\pi\) stacking interaction of the phenoxy or benzyloxy group.
Selective estrogen receptor modulators (SERMs) are a new category of therapeutic agents that are used for the prevention and in the treatment of diseases such as osteoporosis and uterus and breast cancers \[251, 252\]. They are known to have high affinity for ER, but no specific affinity for any other steroid hormone receptors. In addition, SERMs are known to stimulate estrogenic actions (ER agonist) in tissues, such as the bone, liver, and cardiovascular system but block estrogen action at other sites (ER antagonist) where stimulation is considered undesirable, such as the breast and uterus \[253–257\]. This agonistic or antagonistic activity causes different conformational changes of the receptors particularly at the helix 12 \[257–259\], resulting in activation (transactivation) or repression (transrepression) of the estrogen target genes \[258\]. Examples of drugs classified as SERMs are:
estrogen metabolites, clomiphene, tamoxifen, toremifene, idoxifene and droloxifene \cite{259-261}. Tamoxifen is the most widely used hormonal therapy for breast cancer today.

Compound \textbf{43 (Fig.11)} belongs to a new category of SERM called benzopyranone molecules or coumarin-based SERM, producing similar effects as other SERMs indicated above \cite{262, 263}. However, it possesses a different structural feature from those of an ideal SERM such as tamoxifen and thus may induce a different conformational change to the ER, resulting in different cofactor recruitment \cite{264-266}. Furthermore, compound \textbf{43} does not activate genes through estrogen response element (ERE). It is known to bind with high affinity through ER\textsubscript{\(\alpha\)}, effectively antagonize estrogen action in ER\textsubscript{\(\alpha\)}-expressing breast cancer cells by inhibiting IL-6 and GM-CSF gene expression and thus functions as potent antiestrogen in both in vitro and in vivo models of breast cancer \cite{263, 267}. Previous studies have demonstrated that compound \textbf{43} acts as an antiestrogen in the breast and potently inhibits estrogen-dependent MCF-7 proliferation with similar IC\textsubscript{50} value to tamoxifen \cite{267}. Furthermore, compound 43 is more potent than estrogen, behaved as an estrogen agonist in the bone cells in vivo, as effective as raloxifene in decreasing the formation of osteoclastlike cells and partially protected animals against ovariectomy-induced osteopenia \cite{262}. In vitro U2OS/IL-6 and MCF-7 assays revealed that 1) movement of the basic amine side chain on the phenyl group at C-4 to the C-3 in the 4-phenyl of the benzopyranone series provided a significant improvement in antiproliferative activity; 2) manipulation of the side chain was effective in mimicking the hinge substituent found in the benzopyranone 4-benzyl series and 3) an extension of the side-chain length improved receptor-binding affinity \cite{268}. Tetracyclic benzopyranone ring system such as
benzopyranobenzopyran (44, n=1), benzopyranobenzoxa-pane (45, n=2) and benzopyranobenzoxacane (46, n=3) are excellent in mimicking natural ligands as estrogen receptor modulators \cite{269}. These molecules differ from ideal SERMs in that they do not contain the basic side-chain group critical for providing selective tissue antagonist properties as seen with tamoxifen and raloxifene \cite{270}.

Study aimed at the development of newer SERMs revealed that 3-substituted coumarin (47) \cite{271} and coumestrol (48) \cite{272} possess estrogenic activity. Compound 48, a plant derived tetracyclic coumarin, bears similar chemical features as estrogen attributed to its apparently crude mimicry of the steroid skeleton, thus making it possible for the coumarin moiety of the molecule to mimic the A/B ring of estrogen. SAR studies of the structure and relative binding affinities (RBAs) of various 3-substituted coumarins revealed that substituents at positions 3 and 7 resulted to an increase in RBA for the ERα \cite{273–275}. In comparison to estradiol, 3-phenyl-4-ethyl-7-hydroxycoumarins and 3-(4-hydroxy-phenyl)-4,7dihydroxycoumarin showed weak RBA and lack of selectivity toward both ERs. Furthermore, substitution with a second phenyl group at position 4 resulted in 3,4diphenyl-7-hydroxycoumarin showing an increase in RBA to both ERs but with more selectivity for ERα than ERβ \cite{276}.
Structures of coumarin-based SERMs.

"Fig. (11)"

(43), SP500263

44 (n = 1, R₁ = R₂ = OH)
45 (n = 2, R₁ = R₂ = OH)
46 (n = 3, R₁ = R₂ = OH)

(47)

(48), coumestrol
5.2.4 - Coumarin-Estrogen Conjugates:

There is an over-expressed ER in breast tumor cell in the earlier stage and during hormonal treatment \(^{[277, 278]}\). The non-selectivity and acute toxicity of many antitumor agents have been the major deterrent in their usage for treating human cancer \(^{[279]}\). Among the current cancer therapy focusing on the improvement of drug selectivity, conjugation of cytotoxic drug components to a carrier with selectivity toward the tumor tissues has proven to be an effective strategy in the development of efficient antitumor
drugs with high therapeutic indices [280–285]. Studies have shown that coupling of cytotoxic agent with steroid hormones results in improvement of antitumor activity and in the target selectivity of the conjugate as the result of sufficient binding to the ER, allowing selective accumulation of the conjugates in ER-rich cells [285–290]. During the past decades, the application of bioconjugates (i.e. biomolecules bearing unnatural organic structures) in molecular and cell biology has significantly increased [148].

We have recently extended this novel concept of bioconjugation involving 3-substituted coumarins and estradiol (49–51) (Fig. 13) to show antiproliferative activity in NCI-7 human breast cancer cell lines. Comparisons of the GI50 values among the conjugates showed that conjugate 49 has the highest antiproliferation activity against MDA-MB-435 breast cancer cell lines while conjugates (50–51) displayed the highest antiproliferative activities against MDA-MB-231/ATCC. As far as the distinction between noninvasive and invasive breast cancer cell lines, overall conjugate 50 appears to be active against both types while conjugate 49 has the least inhibitory activities against noninvasive MDA-MB-231/ATCC and NCI/ADR-RES cell lines among the conjugates. Moreover, conjugate 49 was surprisingly inactive against the estrogen receptor enriched MCF-7. In general, it was shown that cytotoxicity occurred at around 100 µM for all of the conjugates.

It was also observed that conjugate 50 displayed the most cytostatic properties based upon TGI values being less than LC50 values.
"Fig (13)"

Structures of coumarin-estradiol conjugates.

5.3-SYNTHESIS OF COUMARIN DERIVATIVES WITH ANTICANCER ACTIVITY:

Coumarins have been the subject of extensive studies because of their interesting biological activities and have, in fact, been used as therapeutic agents for the treatment of various diseases including breast cancer. There are various methods for preparing coumarin derivatives; these include the classic Pechmann, Claisen, Perkin, Knoevenagel, and Wittig reactions [291, 292], to mention but a few. Recently, Musa [293] explored the intramolecular Baylis-Hillman reaction reported by Drewes et al. [294] as an alternative route to the synthesis of substituted coumarins, which has been further explored in the synthesis of coumarin-estrogen conjugates as anticancer agents. There is, nevertheless, a continuing interest in the
synthesis of these important coumarin systems. Of particular interest to this review, the synthesis of only those coumarins with anticancer potentials, namely the coumarin sulfamates, benzopyrano- benzopyran ring systems, coumarin 3-carboxamides, coumarin 3-sulfonamides and some others that have been outlined here.

**5.3.1- Coumarin Sulfamates :-**

The Pechmann reaction (Scheme 53), widely used method for preparing coumarins (54) in good yield, involves reacting phenol (52) with β-oxo ester (53) in the presence of either homogeneous acid catalysts e.g. sulfuric [291, 295], phosphoric and trifluoroacetic acids [296], and Lewis acids, or heterogeneous catalysts e.g. Nafion-H, zeolite-HBEA and other solid acids [297]. The reaction is considered to involve the following steps: (i) addition across the double bond of the enolic form of the β- keto ester; (ii) ring closure; and (iii) dehydration [298].

Previous studies demonstrating the estrogenicity of coumestrol (48) led to other coumarin ring systems being explored as an alternative phenolic-based non-steroidal sulfamate compound. Wool et al. reported the synthesis of bicyclic and tricyclic coumarin sulfamates, e.g. COUMATE (24) (Fig. 6), a non-estrogenic active site-directed E1-STS inhibitor [181, 207] via the Pechmann reaction between resorcinol and either of the corresponding Lketooester (55–57) in presence of an equimolar mixture of trifluoroacetic acid and concentrated sulfuric acid as the condensing agent to afford the coumarins (59–61) in > 60% yield [299, 300] (Scheme 54). The lowest yield (25–33%) was obtained for tricyclic coumarin (61, n= 6), which was attributed to the ring size of its starting 8-membered cyclic Lketooester.
synthesis of coumarine by Pechmann reaction

reagents and conditions: (i) resorcinol (58), CF₃COOH/conc. H₂SO₄ (1:1), 0°C; (ii) NaH/DMF, H₂NSO₂C₁; (iii) K₂CO₃/(Bu)₄N⁺Cl⁻·xH₂O/H₂O/CHC₁₃, r.t.
Perkin reaction, involves heating an O-hydroxybenzaldehyde with acetic anhydride in the presence of sodium acetate at a high temperature (ca. 200°C) to afford a trans-cinnamic acid, followed by irradiation or treatment with iodine and then cyclization to afford the coumarin. This reaction is also carried out by reacting acetic anhydride and salicylaldehyde in the presence of trimethylamine as the base catalyst.[301] However, the obvious advantage is that the formation of isomeric chromones is not possible, as is the case with the Pechmann reaction.[302]

Efforts to synthesize the unsymmetrical tetracyclic benzopyranobenzopyran ring system (74), novel selective estrogen receptor modulators (SERMs)[303–305], by Kanojia et al. led to the synthesis of 4-methyl-3,7-substituted coumarins (69) as the key intermediates, via base-catalyzed Perkin condensation reaction in moderate to good yield (Scheme 55).[304] These were furnished by reacting a mixture of 2-hydroxyacetophenones (67) and 2,4-dimethoxyphenylacetic acid (68) in the presence of triethylamine in refluxing acetic anhydride. The next step, which is known as the key step is said to involve the conversion of the 4-methyl functional group of coumarin (69) to the 4-halogenated methyl moiety, followed by ring closure to give the benzopyranobenzopyran compounds.
Reagents and conditions: (i) Et₃N, Ac₂O/reflux; ii) pyridine, HC1/200°C; iii) Ac₂O/ pyridine; iv) NBS /benzoyl peroxide, CCl₄/hv; v) K₂CO₃/MeOH/acetone; vi) LiHMDS/ THF/−32°C, then NBS/THF/78°C; vii) BBr₅/ DCM, then NaOH/H⁺.

5.3.3- Coumarin 3-Carboxamides :-

Various coumarins (76) have been prepared via Knoevenagel condensation reaction (Scheme 56) by reacting 2-hydroxybenzaldehydes (65) with activated methylene compounds (75) in the presence of an amine (e.g piperidine) [302]. Two different mechanisms have been proposed for Knoevenagel reaction [306]: i) formation of an imine or iminium salt,
followed by reaction with the enolate of the active methylene compound, then elimination of the amine and intramolecular ring closure to give the coumarin, ii) attack by the carbanion formed from the deprotonation of the active methylene compound by the amine, on the carbonyl group to give the intermediate follow by proton transfer, and ringclosure via acyl substitution, and finally dehydration to give the coumarin.

Intrigued by the recent discovery demonstrating that coumarin-3-carboxamide (81) inhibits the growth of cancer cell lines by up-regulating the activity of c-Jun NH$_2$ terminal kinase 1 (JNK1) $^{[307]}$, Reddy et al. explored two novel routes to synthesize it via Knoevenagel condensation reaction. These synthetic routes involved: i) the condensation of 3-anilino-3-oxopropionic acid (80) with substituted salicylaldehydes (65) in glacial acetic acid in the presence of a catalytic amount of benzylamine, to afford (81) in 60–80% isolated yield $^{[308, 309]}$, and ii) condensation of methyl 3-anilino-3-oxopropionates (79) with substituted salicylaldehydes (65) in the presence of piperidine in ethanol to give coumarin (81) in 68–88 % isolated yield (Scheme 57) $^{[308]}$

"Scheme (56)"

Knoevenagel reaction.
Some coumarin-3-sulfonamides have shown to be potent inhibitors of various cancer cell lines, which are used in the treatment of diseases arising from abnormal cell growth and proliferation \cite{309,310}. Previously, coumarin-3-sulfonamides was synthesized via the condensation of coumarin-3-sulfonyl chloride with different aromatic amines, which posed some limitations as the result of the difficulty of introducing a variety of substituents on the aromatic rings, thus making it impossible to create a library of new broadly un-substituted coumarin-3-arylsulfonamides \cite{312-316}. Most recently, Reddy et al. \cite{307} reported the synthesis of coumarin-3-sulfonamides (84) in their investigation involving the antitumor activity of novel compounds bearing coumarin and sulfonamide entities via Knoevenagel condensation reaction. This reaction involved reacting methyl-2-chloro-sulfonyl acetate with aromatic amines to afford intermediates (82), which were then hydrolyzed to anilinosulfonylacetic acids (83) and finally, condensation with substituted salicylaldehydes (65) in the presence of glacial acetic acid and a catalytic amount of benzylamine afforded coumarin-3-sulfonamides (84) in quantitative yields. An alternative route for the synthesis of (84) was also reported that involved the condensation of methyl anilinosulfonylacetates (82) with substituted salicylaldehydes (65) in the presence of piperidine and ethanol (Scheme 57) \cite{307}. 
Scheme (57): Reagents and conditions: i) Et₃N, CH₂Cl₂, 0°C to rt; ii) 10% NaOH, HCl; iii) PhCH₂NH₂, HOAc, reflux, iv) piperidine, ethanol, reflux 1 h

b. Reagents and conditions: (i) C₅SO₂CH₂COOCH₃, triethylamine/THF, N₂, rt, 3 h; (ii) 10% NaOH in H₂O; (iii) CH₃COOH, C₆H₅CH₂NH₂; (iv) piperidine, ethanol, reflux, 5 min.
5.3.5- Miscellaneous :-

These methods involved the formation of isolable intermediate followed by cyclization using either acid or coupling agents to afford the coumarin derivatives. For example, McKe et al. [316] reported the synthesis of coumarin-based benzopyranone compounds and their salts used for treating bone-resorption disease, cancer, arthritis via the following steps: i) the reaction of 3-methoxyphenol (86) and 4-hydroxyphenylacetic acid (85) in the presence of boron trifluoride in diethyl etherate (Fries reaction) to give (87) in 40–50% yield; ii ) coupling reaction using 1,1’-carbonyl-diimidazole to afford the desired coumarin (89) in 10– 90 % yield; iii) the introduction of the amino basic side-chain to yield coumarin-7-methyl ether (90) in 30–70% yield; and iv) demethylation of 90 using HBr to afford 60–75% of the desired coumarin (91) (Scheme 58).

Recent investigation by our research group involving the antitumor activity of coumarin derivatives revealed that the conjugation of coumarin substrate to 17β- estradiol, afforded coumarin-estrogen conjugates, which demonstrate growth inhibitory activities in various breast cancer cell lines. Using the generality of the methodology outlined by Drewes et al., [317] which was further explored and reported , various 3-substituted coumarin quaternary salts were prepared via the intramolecular Baylis-Hillmann reaction using DABCO as a catalyst and then coupled to 17β- estradiol and estrone oxime to afford coumarin-estrogen conjugates (49–51), (Sch.59)
Scheme (58) : Reagents and conditions: i) BF3 diethyletherate (Fries reaction); ii) CDI, K$_2$CO$_3$, DMAP, 10–90%; iii) K$_2$CO$_3$, l-(2-chloroethyl)pyrrolidine, 30–75%; iv) 30–50% HBr, AcOH

Scheme (59) : Reagents: i) Acrylo chloride, NaH, reflux; ii) DABCO, CH$_2$C12, rt, iii) K$_2$CO$_3$, CH$_3$CN, reflux, overnight, iv) NH$_2$ OH, THF, reflux.
Table (4) : some Biologically Active Coumarins

<table>
<thead>
<tr>
<th>Examples</th>
<th>Biological Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image14.png" alt="Coumarin 14" /> R = H, <img src="image15.png" alt="Coumarin 15" /> R = CH₃, <img src="image16.png" alt="Coumarin 16" /> R = CO₂Et</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td><img src="image17.png" alt="Coumarin 17" /> <img src="image18.png" alt="Coumarin 18" /></td>
<td>Anti-HIV (Reverse transcriptase inhibitors)</td>
</tr>
<tr>
<td><img src="image19.png" alt="Coumarin 19" /> R = CH₂, R¹ = H₂NCO, <img src="image20.png" alt="Coumarin 20" /> R = CH₂, R¹ = C₆H₄N</td>
<td>Antibiotic and Antibacterial (DNA gyrase inhibitors)</td>
</tr>
<tr>
<td><img src="image21.png" alt="Coumarin 21" /> <img src="image22.png" alt="Coumarin 22" /></td>
<td>Anticancer (Breast cancer, Stomach cancer, Colon cancer and Renal cancer)</td>
</tr>
</tbody>
</table>
5.4- Furanocoumarins as potent chemical defenses:

Natural coumarins have a wide spectrum of activity ranging from the beneficial to the highly toxic. Generally, the furanocoumarins are more biologically active than the other types.

Furanocoumarins are toxic compounds found primarily in species of the Apiaceae and Rutacea[^318]. They come in a variety of flavors and have adverse affects on wide variety of organisms, ranging from bacteria to mammals. Some of the furanocoumarins are photoactive--their toxicity is enhanced in the presence of ultraviolet radiation.

One of the better-studied modes of toxicity involves the binding of furanocoumarins to DNA. However, furanocoumarins have also been shown to interact with protein and lipids.

5.4.1- Biosynthesis of Furanocoumarins:

Involves contributions from two pathways, the phenylpropanoid pathway and the mevalonic acid pathway. The immediate precursors for furanocoumarin synthesis are umbelliferone and isoprene[^319]. Two categories of furanocoumarins are produced; the linear furano-coumarins have the furan ring in line with the benz-2-pyrene nucleus, while the angular furanocoumarins have the furan ring oriented at an angle to the nucleus.
5.4.2 Coevolution between a herbivore and its host plant:

The furanocoumarins found in wild parsnip play a dominant role in resistance of this plant to its principal enemy the parsnip webworm. The interaction between wild parsnips, *Pastinaca sativa*, and the parsnip webworm, *Depressaria pastinacella*, is mediated by a group of toxic compounds called furanocoumarins. The furanocoumarins play a dominant role in resistance of this plant, wild parsnips, to its principal enemy the parsnip webworm, as furanocoumarins are found throughout the parsnip plant, including its reproductive parts, which are the favorite food of the parsnip webworm. Few herbivores are capable of coping with the high concentrations of furanocoumarins found in wild parsnips. Thanks to
a highly efficient detoxification system parsnips webworms \[^{[323]}\] are well adapted to coping with these compounds.

People, as well as insects, can suffer from exposure to these compounds. \[^{[324]}\]“Celery picker's itch” and "bartender's itch" are two maladies suffered when humans come into contact with furanocoumarin-containing celery plants or the oil of lime peels.

### 5.4.3- symptoms of Celery picker's itch & bartender's itch :-

(1) The symptoms are dramatic, In the most severe cases, blisters will develop.
(2) In less severe cases, the skin will become hyperpigmented and can remain so for several weeks.

Picture (1): symptoms of Celery picker's itch & bartender's itch
A Special Emphasis on Coumarin Derivatives:

"Fig (15)"

Representative bio-active natural coumarins

(+)-Calanolide A, (Fig.15) (+)-[10R,11S,12S]-10,11-trans-dihydro-12-hydroxy-6,6,10,11-tetra methyl-4-propyl-2H, 6H-benzo [1,2-b:3,4-b’:5,6-b’] tripyran-2-one is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against HIV-1 \(^{1325}\). This compound was first isolated from a plant *Calophyllum lanigerum* in Malaysia. Due to low availability of naturally occurring (+)-calanolide A, a total synthesis of this polycyclic coumarin was developed to provide material for preclinical and clinical research\(^{10a}\). Only (+)-calanolide A accounted for anti-HIV activity, which was similar to the data reported for the natural product while (−)-calanolide A was inactive.
Patil et al.[326] reported the isolation of (+)-inophyllum B from C. Inophyllum which is the most active component for inhibition against HIV-reverse transcriptase. (+)-Cordatolide A, isolated from the light petrol extract of the leaves of C. cordatooblangum in 1985[327], is a novel tetracyclic coumarin. Its structure and properties are similar to (+)-calanolide A[328].

Ayapana triplinervis was first discovered in the late 1930s from the plant Ayapana triplinervis, it was reported to have pronounced blood-thinning or anticoagulant actions[329]. Ayapana also contains a coumarin named hernarin (7-methoxycoumarin) hence the plant is used in herbal medicine as an anti-tumor remedy. Recently, it was found that this chemical is toxic to cancer cells including multi-drug resistant cancer cells and leukemic cells[330].

Carbochromen is a coronary vasodilator drugs and is capable of increasing local myocardial blood flow and decreasing myocardial metabolic heat production both in the normal canine myocardium and in the myocardium rendered ischaemic by acute ligation of a coronary artery[331].
Marine alkaloids containing coumarin skeleton

Pyrrolocoumarins are of considerable pharmacological relevance and occur in a variety of natural products. A chromeno[3,4-b]pyrrol-4(3H)-one core structure occurs, for example, in the marine alkaloids Ningalin B and Lamellarin D (Fig:16) which exhibit HIV-1 integrase inhibition, immunomodulatory activity and cytotoxicity\[^{[332]}\].

5.6- Photosensitive Coumarins:-

5.6.1-(A) 3-[4-bromoethyl] phenyl-7-(diethylamino)- coumarins:

Several coumarins were found to have the property of fluorescence. Notable among them are 3-[4-bromoethyl] phenyl-7-(diethylamino)-coumarins as fluorescent derivatization reagents for carboxylic acid in High Pressure Liquid Chromatography\[^{[333]}\].
Coumarins fused to naphthopyrans were reported as fluorescent brighteners\textsuperscript{[334]}

A series of new photochromic fused-naphthopyrans with an alkyl bridge between the pyran ring and the naphthalenic core was synthesized in several steps from 4-(bromomethyl)benzocoumarin. The presence of the alkyl bridge in these new fused-naphthopyrans prevents the formation of one long-lived photoisomer and therefore has a dramatic effect on their photochromic properties.
UV irradiation of common naphthopyrans gives rise to two isomeric colored photoisomers, one of which fades very slowly and is responsible for a persistent residual color. UV excitation of these new uncolored fused-naphthopyrans leads to the formation of only one colored photoisomer that fades completely to the uncolored state in few seconds/minutes following a monoexponential decay law, thus avoiding the problem of the residual coloration typically observed with naphthopyrans.

Fig (18)
Coumarins fused to naphthopyrans as fluorescent brighteners
REFERENCE
REFERENCES


[73] Schenck et al., Angew. Chem. 73, 764 (1961).


Egan D, O'Kennedy R, Moran E, Cox D, Prosser E, Thornes RD. [139]


