The work incorporated in the thesis deals with the synthesis of various heterocyclic substituted, heterocyclic fused and aromatic fused coumarin derivatives, such as bipyridyl coumarins, pyrido/quinolino fused coumarins, pyridyl/quinolyl carbonyl substituted coumarins, coumarinyl substituted pyrido fused coumarins, pyridyl substituted benzo[c]coumarins, quinolinyl-pyrazolyl substituted coumarins, etc. Hence, a brief review of some aspects of coumarins, heterocyclic substituted and heterocyclic fused coumarins is presented in the following sections.

1.1 Introduction, Nomenclature and Occurrence

Coumarins are the best known aromatic lactones\(^1\). The isolation of coumarin was first reported by Vogel\(^2\) in Munich in 1820. He associated the pleasant odour of the tonka bean from Guiana with that of clover, *Melilotous officinalis*, which gives rise to the characteristic aroma of new-mown hay. Vogel then concluded that the long colourless crystals which he discovered on slicing open tonka beans and which crystallized as glistening needles from aqueous alcohol were identical with similar crystals he obtained, albeit in much lower yield, by extracting fresh clover blossoms\(^3\). The name coumarin originated\(^4\) from a Caribbean word ‘coumarou’ for the tonka tree, which was known botanically at one time as *Coumarouna odorata* Aubl. Coumarin is now well accepted trivial name. The IUPAC nomenclature of the coumarin ring system is 2\(H\)-1-benzopyran-2-one (1).

![Coumarin Ring System](image)

The coumarin ring system has an easy acceptability in the biological system compared to its isomeric chromones and flavones.
nucleus and is widely distributed in nature. An excellent account of these naturally occurring coumarins is presented by R D H Murray and S A Brown.

1.2 General methods for the synthesis of coumarins

There are several methods for building up the coumarin ring system. The key step in many cases has been the formation of the pyrone ring. Phenols, o-hydroxy benzaldehydes and acetophenones are requisite precursors for preparing coumarin ring. Some of these important methods are outlined below.

1.2.1 Synthesis of coumarins based on phenols:

(1) The Pechmann reaction is the most well known and an important method with extensive applications. It involves reaction of phenols with β-ketoesters (ethyl acetoacetate or malic acid) to give variety of coumarin derivatives.

Variety of reagents have been used for this condensation and the reaction has been studied thoroughly using Lewis acid, ionic liquids, CAN, HClO₄.SiO₂, sulfated zirconia, Bi(NO₃)₃.5H₂O, FeCl₃, sulfonic acid nanoreactor, oxalic acid, ClSO₃H, TiCl₄, SnCl₂.2H₂O, etc.

(2) V R Shah et al have developed a method which has general applicability for the synthesis of 4-hydroxy coumarins. In this method variety of phenols are condensed with malonic acid in the presence of phosphorous oxychloride and zinc chloride to afford 4-hydroxy coumarins.
(3) The synthesis of 3-methyl coumarins is reported by B Gopalan\textsuperscript{26} in which Claisen rearrangement has been utilized. Phenol on reaction with methyl-\(\alpha\)-bromomethyl acrylate in alkaline conditions gives \(\alpha\)-aryloxyethyl acrylate which is heated in o-dichlorobenzene/triethylamine to afford the 3-methyl coumarin.

(4) R Hekmatshoar et al\textsuperscript{27} have synthesized various 4-carboxymethoxy substituted coumarins by reacting appropriate phenols with dimethyl acetylenedicarboxylate and triphenylphosphine in refluxing dichloromethane.

(5) A novel method of synthesizing coumarins is reported by E Fillion et al\textsuperscript{28} in which 5-(methoxymethylene)meldrum’s acid is reacted with phenols in the presence of Yb(OTf)\textsubscript{3} catalyst.
Kitamura et al\textsuperscript{29} have reported the synthesis of coumarins by reacting phenols and $\alpha,\beta$-unsaturated acid esters in the presence of Pd(OAc)$_2$ and K$_2$S$_2$O$_8$ in CF$_3$CO$_2$H.

\[
\frac{\text{PhOH}}{\text{PhOH}} + \frac{\text{R}_1\text{COOEt}}{\text{R}_1\text{COOEt}} \xrightarrow{\text{Pd(OAc)$_2$ \& K$_2$S$_2$O$_8$ in CF$_3$CO$_2$H}} \frac{\text{PhOCO}}{\text{PhOCO}}
\]

Kalyanam et al\textsuperscript{30} have prepared coumarins in a single-step by condensation of appropriately substituted phenols with acetylenic esters using catalytic amounts of indium chloride in the absence of solvent.

\[
\frac{\text{PhOH}}{\text{PhOH}} + \frac{\text{R}_1\text{COOEt}}{\text{R}_1\text{COOEt}} \xrightarrow{\text{InCl$_3$}} \frac{\text{PhOCO}}{\text{PhOCO}}
\]

### 1.2.2 Synthesis of coumarins based on o-hydroxy benzaldehydes or acetophenones:

1. The first and the foremost example of this method is the famous \textit{Perkin reaction}\textsuperscript{31}. In the classical reaction, salicylaldehyde is heated with acetic anhydride in the presence of sodium acetate to give coumarin.

\[
\frac{\text{PhCHO}}{\text{PhCHO}} \xrightarrow{\text{NaOAc \& Ac$_2$O}} \frac{\text{PhOCO}}{\text{PhOCO}}
\]

The reaction has been further extended to synthesize 3-phenyl coumarins\textsuperscript{32} and 3-phenoxy coumarins\textsuperscript{33}.

\[
\frac{\text{PhCHO}}{\text{PhCHO}} + \frac{\text{RCOO}}{\text{RCOO}} \xrightarrow{\text{NaOAc \& Ac$_2$O}} \frac{\text{PhOCO}}{\text{PhOCO}}
\]

R= Ph, OPh

2. Good yields of 3-substituted coumarins are obtained by the \textit{Knoevenagel reaction}\textsuperscript{34}. Here, o-hydroxy benzaldehydes are condensed with active methylene compounds like diethyl malonate, ethylcyano-
acetate and ethyl acetoacetate in the presence of piperidine catalyst with or without ethanol as solvent.

(3) Another novel method for the synthesis of coumarins involves Wittig reaction between substituted o-hydroxy benzaldehydes or o-hydroxy acetophenones/benzophenones and substituted carbethoxy methylene triphenyl phosphoranes. The method has general applicability and the yields are good.

R₁ = H, CH₃, Ph

R₂ = H, CH₃, C₆H₅, CH₂Ph, CH₂CH=CH₂

Kaye et al have reported the synthesis of 3-chloromethyl coumarin by reacting salicaldehyde and t-butyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and treating the resultant Baylis-Hillman adduct with HCl.

H S P Rao et al have reported the facile synthesis of 3-arylcoumarins from condensation of α-arylketene dithioacetal (AKDTA) and 2-hydroxy benzaldehyde with a catalytic amount of piperidene in refluxing THF.
(6) A convenient one-pot synthesis of 4-hydroxy coumarin is reported by Jae-Chul Jung et al\(^6\) in which o-hydroxy acetophenone is reacted with acylating reagents such as phosgene, dimethylcarbonate or diethylcarbonate in the presence of stoichiometric amount of base like NaH or NaOEt.

(7) Solvent free syntheses of coumarin via Pechmann and Knoevenagel condensation reactions are reported by T Sugino and K Tanaka\(^7\).

(8) F Fringuelli et al\(^8\) have investigated one-pot synthesis of 3-carboxycoumarins via consecutive Knoevenagel and Pinner reactions.

(9) A novel approach towards the synthesis of coumarins has been reported by D C Dittmer et al\(^9\). Authors have synthesized coumarins by cyclizing \(\alpha\)-halo esters of salicylaldehyde, o-hydroxy acetophenone and methyl salicylate in the presence of sodium or lithium telluride. The \(\alpha\)-
halo esters were prepared by reacting salicylaldehyde, o-hydroxy acetophenone and methyl salicylate with α-halo acid halide.

\[
\begin{align*}
\text{OH} & \quad \text{R}_2\text{CHXCOX} \\
\text{O} & \quad \text{R}_1
\end{align*}
\]

\[
\begin{align*}
\text{R}_1 & = \text{H, Me, OMe} \\
\text{R}_2 & = \text{H, Me, Ph} \\
\text{R} & = \text{H, Me, OH}
\end{align*}
\]

### 1.2.3 Miscellaneous preparation of coumarins

**1.** A new method of synthesizing coumarins using arenes and palladium catalyst in 1:1 trifluoroacetic acid and dichloromethane is reported by *J Chengguo et al*\(^{45}\) and *Kelin Li et al*\(^{46}\).

\[
\begin{align*}
\text{Pd(OAc)}_2, \text{5 mol}\% \\
1:1 \text{TFA/DCM}
\end{align*}
\]

**2.** Recently, *S Higashida et al*\(^{47}\) have investigated a novel route of synthesizing coumarins in which phenanthrene was converted into coumarin compounds by a TiO\(_2\)–photo catalyzed reaction in an acetonitrile solution containing 8 wt % water and molecular oxygen.

\[
\begin{align*}
\text{TiO}_2, \text{hv} \\
\text{CH}_3\text{CN, H}_2\text{O, O}_2
\end{align*}
\]

**3.** *D K Rayabarapu* and *C H Cheng*\(^{48}\) have reported synthesis of benzocoumarin (3), in which 7-oxabenzonorbornadiene (1) was treated with methyl butyn-2-oate (2) in the presence of NiBr\(_2\) bis(diphenylphosphino)ethane and zinc metal powder in acetonitrile at 80°C.
A K Chatterjee et al\textsuperscript{(4)} have reported the synthesis of coumarins by ring closing metathesis of (3) in the presence of second generation ruthenium catalyst.

Y Yamamoto et al\textsuperscript{(5)} have documented CuOAc catalysed reaction of methyl phenyl propiolates having a MOM-protected hydroxy group at the ortho position with various arylboronic acids in MeOH at ambient temperature, resulting in the formation of 4-aryl coumarins in high yields after the acidic workup.

L Rong et al\textsuperscript{(6)} have reported synthesis of 4-aryl-7,7-dimethyl-5-oxo-3,4,5,6,7,8-hexahydrocoumarin derivatives through a one-pot reaction of aromatic aldehydes, 2,2-dimethyl-1,3-dioxane-4,6-dione and 5,5-dimethyl-1,3-cyclohexanedione, in the presence of triethylbenzyl ammonium chloride (TEBA) under solvent-free conditions using grinding methods.
1.3 Reactions of coumarins

(1) Action of alkali

All coumarins, being lactones, react with alkalis. Their reactivity towards base and the nature of products formed depends on the structure of the particular coumarin and the rigor of reaction conditions. The initial action of the alkali is always opening of the lactone ring and the formation of a salt of coumarinic acid. Acidification of this salt regenerates original coumarin. The opening of lactone ring by alkali is affected by substitution. 7-Methoxy coumarin is much harder to hydrolyze than coumarin; 7-hydroxy coumarin is still harder than 7-methoxy coumarin as it at once forms the negatively charged phenolic ion\(^{52,53}\).

![Reaction with alkali](image)

(2) Halogenation

Addition of bromine to the 3,4-double bond of coumarin, followed by facile loss of hydrogen bromide gives 3-bromo coumarin\(^{54}\). The latter product can also be obtained using N-bromo succinimide.

![Halogenation](image)

The presence of 4-alkyl group decreases the stability of dibromide\(^{55}\). When coumarin is treated with bromine in carbon disulfide at 140°C or in the presence of iodine at 170°C it gives 3,6-dibromo coumarin and 3,6,8-tribromo coumarin respectively\(^{56}\). 4-Halogeno coumarins are made by treating 4-hydroxy coumarin with phosphorus pentahalide and this becomes the only method for introducing halogen at 4-position unless negative groups are present in the benzene ring\(^{57}\).
Chlorination of coumarins is quite similar to bromination. Iodo compounds cannot be made by direct iodination but must be prepared by synthesis. Coumarins when treated with iodine give addition compounds.

(3) Nitration

Coumarin on nitration gives mainly 6-nitro coumarin along with formation of 8-nitro coumarin. On further nitration at 100°C, 6-nitro coumarin gives 3,6-dinitro coumarin and 8-nitro coumarin gives 6,8-dinitro coumarin. The ease of nitration increases with introduction of alkyl groups, especially, in 4-position. To obtain mono-nitro coumarin, theoretical amount of nitric acid must be employed. The presence of hydroxyl groups in the aromatic part makes this ring more like phenol and more susceptible to nitration. The nitration of coumarin with benzoyl nitrates is reported to give 5-nitro coumarin.

(4) Sulphonation

Coumarin when treated with fuming sulfuric acid at 100°C gives coumarin-6-sulphonic acid. Further reaction with fuming sulfuric acid for 1-2 hours at 150-160°C gives coumarin-3,6-disulphonic acid.

(5) Fries rearrangement and Friedel-Crafts reaction

Coumarin with ketone group in the aromatic ring may be prepared directly by Friedel-Crafts reaction on hydroxy coumarin, or better by the Fries rearrangement. In the 5-hydroxy coumarin series, 5-hydroxy-6-acetyl coumarins are produced, whereas 7-hydroxy coumarin gives 7-hydroxy-8-acetyl coumarin together with a little amount of 6-acetyl derivative. If 8-position is substituted, the 6-acetyl derivative is the main product.

(6) Claisen rearrangement

Coumarin with hydroxyl group in the benzene ring behaves as phenol and undergoes all the typical reactions of phenols, including Claisen rearrangement. 4-Methyl-7-allyloxy coumarin rearranges to 8-position.
(7) **Photo dimerization**

The photochemical $2\pi + 2\pi$ dimerization of unsaturated organic molecules is a well-known process in organic photo-chemistry$^{72}$. Among the compounds investigated, coumarin and its derivatives have attracted considerable interest, in part because of their biological and photobiological importance$^{73}$. Head-to-head dimers, head-to-tail dimers as well as syn and anti dimers may be formed during reaction.

The formation of dimers depends on the solvent system and concentration. A study of the photodimerization of a variety of coumarin derivatives was investigated in solution$^{74}$ as well as in solid systems$^{75}$ or anchored to a surface$^{76}$. Recently S Karthikeyan et al$^{77}$ proposed highly selective photodimerization of coumarins within a water-soluble nano reaction vessel. T Wolff et al$^{78}$ demonstrated the selectivity in the photodimerization of 6-alkyl coumarins.

In addition to the above reactions, coumarins also undergo some miscellaneous reactions. Coumarins when treated with phosphorus pentasulfide give thiocoumarins$^{79}$ and are used to prepare the oxime and phenyl hydrazone of coumarins. Since, these compounds cannot be prepared directly from coumarin.

Coumarin undergoes *Diels-Alder* reaction with 2,3-dimethyl-1,3-butadiene at 260°C and gives tetrahydro benzocoumarin derivative$^{80}$. 
Similarly, R Girotti et al\textsuperscript{81} have carried out Diels-Alder reaction of 3-substituted coumarins with 2,3-dimethyl-1,3-butadiene in water and in CH\textsubscript{2}Cl\textsubscript{2} under 9 kbar pressure.

M Soltau et al\textsuperscript{82} have investigated the light-induced coumarin cyclopentannelation. The reaction of 4-alk-1-ynlcoumarins with 2,3-dimethylbut-2-ene undergoes tandem cyclization to give tetracyclic (4-hetera)cyclopenta [b,c] acenaphthenes.

### 1.4 Spectral properties of coumarins

#### (1) UV spectroscopy

UV absorption spectra are useful for distinguishing coumarins from chromones. Chromones have a strong absorption at 240-250 nm (log \(\varepsilon\), 3.8), whereas coumarin shows two absorption bands at 274 nm and 311 nm (log \(\varepsilon\), 4.03 and 3.72) which have been attributed to the benzene ring and pyrone ring respectively\textsuperscript{83}. Substitution of methyl group at C\textsubscript{3} leads to a small hypsochromic shift in the 311 nm maximum, leaving the other maximum unchanged. Methyl substitution at C\textsubscript{5}, C\textsubscript{7}, or C\textsubscript{8} leads to a bathochromic shift of 274 nm band but leaves the 311 nm band practically unchanged. The introduction of hydroxyl group into the coumarin nucleus causes bathochromic shift of the principal absorption band. The position of new maxima depends on the ability of the hydroxyl group to conjugate with chromophoric system. 7-Hydroxy coumarin has \(\lambda_{\text{max}}\) 300, 305,
325 nm while 6-hydroxy coumarin has $\lambda_{\text{max}}$ 349 nm. There is a large bathochromic shift for 5,7-dihydroxy coumarin, which has $\lambda_{\text{max}}$ at 282, 326, 372 nm.

(2) **IR spectroscopy**

The $\delta$-lactone carbonyl stretching frequency$^{84,85}$ of a coumarin is usually found in the region 1720-1750 cm$^{-1}$. The exact value depends on the substituents in the benzene ring. The $\delta$-lactone carbonyl frequency is also observed below 1700 cm$^{-1}$ due to intramolecular hydrogen bonding. Such H-bonding is observed in dicoumarol where carbonyl absorbs at around 1660 cm$^{-1}$. There are normally three strong absorption bands in the region 1600-1660 cm$^{-1}$, due to C=C skeletal vibrations in the IR spectra of coumarins which differentiate it from the isomeric chromones, the absorption of which is generally much simpler$^{86}$. Compounds with methoxyl group show bands in the region 1237-1272 cm$^{-1}$.

(3) **$^1$H NMR spectroscopy**

A wide range of NMR techniques have been applied to the structural elucidation of various naturally occurring as well as synthetic coumarins.

The C$_3$-H and C$_4$-H in coumarin lactone ring appear as a pair of doublets centered at 6.1-6.4 $\delta$ and 7.5-8.3 $\delta$ with $J = 9.5$ Hz. The coumarin oxygenated at C$_7$ leads to an increase electron density at C$_3$ compared to parent coumarin and causes the resonance of C$_3$-H to move higher field by 0.7 $\delta$$^{87-89}$. Electron release by C$_5$ oxygenated coumarin has a similar, though smaller effect, since this involves a less favorable ortho-quinonoid electron distribution$^{90}$. The C$_4$-H resonance is found in the region 7.5-7.9 $\delta$ in coumarins lacking a C$_5$ oxygen function. An oxygen or alkyl substituent at C$_5$ shifts the resonance of C$_4$-H downfield by 0.3 $\delta$ (peri effect)$^{90,91}$. C$_3$-H resonates at 6.15 $\delta$ with methyl group at C$_4$ and 6.0 $\delta$ with aryl group at C$_4$$^{92}$. C$_4$-H resonates at ~ 7.65 $\delta$ when there is an alkyl group at C$_3$ and ~ 6.5 $\delta$ in 3-aryl coumarin$^{93}$.

Ether of 7-hydroxy coumarin can readily be recognized as such from their $^1$H NMR spectra. The doublets, $J = 9.5$ Hz, arising from C$_3$-H and C$_4$-H are found centered at 6.23 $\delta$ and 7.64 $\delta$ respectively. In
theory the C₅-H and C₆-H protons should appear as a pair of ortho-
coupled doublets with the C₆-H signal also meta coupled to a C₈-H
signal of similar chemical shift. In practice, C₅-H is found as a
doublet, $J = 9 \text{ Hz}$, at 7.38 δ, downfield from C₆-H and C₈-H signals
which appear as a two-proton multiplet at 6.87 δ. The signals for the
three benzenoid protons are always flanked by the doublets of C₃-H
and C₄-H⁹⁴,⁹⁵.

In coumarins having oxygen function at C₅ and C₇ positions, the
C₆ and C₈ protons are meta related and give rise to a pair of doublets
with $J = 2 \text{ Hz}$ at ~ 6.33 δ. The 7-oxygenated coumarins with alkyl or
alkoxy group at C₈ position show C₅-H signal at ~ 7.3 δ, downfield
from the C₆-H at ~ 6.8 δ, as a pair of doublet, $J = 9 \text{ Hz}$.

In 6,7-disubstituted coumarins, C₅-H and C₈-H appear as
singlets with C₅-H downfield from C₈-H. 7-Oxygenated, 6-alkyl
coumarins, including the linear dihydrofuro and dihydropyrano
coumarins, can easily be distinguished from their C₈-alkylated and
angular analogous. In the spectra of former, C₅-H and C₈-H appear as
singlets at ~ 7.2 δ and ~ 6.7 δ respectively, while in the latter C₅-H and
C₆-H are ortho related and show $J_{5,6} = 9 \text{ Hz}$⁹⁶-⁹⁷.

The NMR shift reagent Eu(fod)₃ complexes with the carbonyl
oxygen atom⁹⁸ of coumarins, apparently in the plane of the ring and
on the C₃-H side of the molecule. It is observed that the signal for
C₃-H showed the greatest shift and that lanthanide-induced shifts
could be expressed by the series 3>4~8>5~7>6, where numbers
represent the position of identical substituents in the coumarin
skeleton. A useful consequence of lanthanide-induced shift is that
signals of similar chemical shift from aromatic protons can be shifted
sufficiently from each other for their coupling to be revealed⁹⁹.

In furo coumarins, the presence of unsubstituted furan ring is
easily recognizable from the pair of doublets $J = 2.5 \text{ Hz}$, which arise
from C₂'-H and C₃'-H. Natural pyrano coumarins are invariably
geminally substituted at C₂ with methyl groups, which resonates as a
six protons singlet at 1.45 δ. The two olefinic protons show a pair
of doublets, $J = 10 \text{ Hz}$ centered at 5.3-5.8 δ (C₃'-H) and 6.3-6.9 δ
(C₄'-H)¹⁰⁰.
**(4) $^{13}$C NMR spectroscopy**

With the availability of Fourier-Transform methods and computer development, $^{13}$C spectroscopy has become a sensitive and powerful tool in the structural elucidation of natural products. A number of publications have been appeared in which complete assignments of $^{13}$C chemical shifts have been presented for hydroxy and methoxy coumarins\textsuperscript{101-103}.

For the unsubstituted coumarin, the carbonyl carbon i.e. C\textsubscript{2} appears at 159.2 $\delta$, the C\textsubscript{3} and C\textsubscript{4} of the lactone ring appear at 115.2 $\delta$ and 142.5 $\delta$ respectively\textsuperscript{102}. The C\textsubscript{5}, C\textsubscript{6}, C\textsubscript{7} and C\textsubscript{8} carbons of the aromatic ring appear at 127.0, 123.2, 130.6 and 115.1 $\delta$ respectively. The fused carbons C\textsubscript{9} and C\textsubscript{10} appear at 152.6 $\delta$ and 117.6 $\delta$ respectively\textsuperscript{104}. The effect of hydroxy and methoxyl group on the benzenoid ring is quite characteristic in that the signal from newly formed quaternary carbon atom is found approximately 30 ppm downfield from the value observed in parent coumarin while the carbons ortho and para to the substituent move upfield by $\sim$13 and $\sim$8 ppm respectively\textsuperscript{105}.

Titanium (IV) chloride has been shown to be a useful shift reagent for coumarin, producing strong downfield shifts for the carbonyl and C\textsubscript{4} carbons with C\textsubscript{3} and C\textsubscript{8a} undergoing small upfield shifts.

***(5) Mass spectrometry***

Fragmentation patterns resulting from electron impact of many natural coumarins have been determined and rationalized and have proved to be of great assistance in structural studies.

The fragmentation pattern of parent coumarin is shown below. It involves loss of CO from coumarin carbonyl group and which is a characteristic feature of the mass spectra of most coumarins. The benzofuran ion decomposed further by consecutive loss of CO and a hydrogen atom\textsuperscript{106}.

\[
\begin{align*}
\text{CO} & \quad \text{CO} & \quad \text{CO} & \quad \text{H} \\
146 (96\%) & \quad 118 (100\%) & \quad 90 (43\%) & \quad 89 (35\%)
\end{align*}
\]
1.5 Heterocyclic substituted coumarins

The literature survey reveals that designing an extra heterocyclic ring on coumarin nucleus has received much attention in the field of synthetic organic chemistry. Hetero moieties like pyridine, quinoline, pyrazole, benzothiazole, triazine, oxazole, etc. have been built up in lactone ring as well as in benzene ring of coumarin. This may be due to the unpredictable activity of such heterocyclic ring systems. Syntheses of some selected heterocyclic substituted coumarins are presented below.

O V Khilya et al\textsuperscript{107} have synthesized 3-(2-pyridyl)coumarins by Knoevenagel condensation of salicylaldehyde with 2-pyridyl acetonitrile and the resulted 2-iminocoumarin were converted to pyridyl coumarins by hydrolysis of the imine.

Francesco Leonetti et al\textsuperscript{108} have synthesized 7-methoxy-4-(4-pyridyl)coumarin by reacting resorcinol and ethyl-3-oxo-3-(pyridin-4-yl)propanoate in the presence of equimolar mixture of H\textsubscript{2}SO\textsubscript{4} and CF\textsubscript{3}COOH followed by methylation as shown in the scheme below.

Concepcion Alonso et al\textsuperscript{109} have synthesized 3-(2-pyridyl) coumarins starting from benzyl-2-(2-pyridyl)acetate as shown below.

\[
\begin{align*}
\text{HO-CH}_2\text{CHO} + \text{CN-CH}_2\text{N} & \xrightarrow{i. \text{ Piperidine}} \text{R-O} \text{N} \text{CH}_2\text{CN} \xrightarrow{ii. \text{ H}_2\text{SO}_4} \text{R-CO} \text{N} \text{CH}_2\text{CN} \\
\text{R} & = \text{H, 6-NO}_2, 6-\text{Cl, 6-Br, 7-OH, 8-OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO-CH}_2\text{CHO} + \text{CN-CH}_2\text{N} & \xrightarrow{1) \text{ H}_2\text{SO}_4 / \text{CF}_3\text{COOH}} \text{OMe} - \text{CH}_2\text{N} \text{CH}_2\text{CN} \xrightarrow{2) \text{ MeI} / \text{ NaH}} \text{R-CO} \text{N} \text{CH}_2\text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & = \text{Cl, Br} \\
\text{R} & = \text{H, 6-NO}_2, 8-\text{NO}_2 \\
\end{align*}
\]
K N Venugopala et al \cite{10} have synthesized carboxamides of 2-amino-4-(6-bromo-3-coumarinyl)thiazole by the reaction of 6-bromo-3-(bromoacetyl)coumarin with N-benzoyl thiourea. They have also reported analgesic and anti-inflammatory activities of these compounds.

\[ \text{Reactions} \]

Jih Ru Hwu et al \cite{11} have synthesized benzimidazole substituted coumarins by the reaction of 3-(chloromethyl)coumarins and benzimidazole-2-thiones in the presence of 35% aqueous NH\(_4\)OH. Some of the compounds were found to be potent anti hepatitis C virus agents.

\[ \text{Reactions} \]

Hasnah Osman et al \cite{12} have synthesized hydrazinyl thiazolyl coumarin derivatives by reacting 3-bromoacetyl coumarin and substituted thiosemicarbazide in chloroform-ethanol as shown below.

\[ \text{Reactions} \]

Thus, varieties of heterocyclic substituted coumarins are reported in literature.
1.6 Heterocyclic fused coumarins

The literature survey reveals that built up of an extra heterocyclic ring on coumarin nucleus, especially on the lactone ring, has also received much attention in the field of synthetic organic chemistry. Hetero moieties like pyridine, furan, pyrazole, oxazole and triazole are fused with coumarin either in aromatic part or in the lactone ring. Several reports are available in literature for the synthesis of heterocyclic fused coumarin derivatives. Syntheses of some selected heterocyclic fused coumarin derivatives reported in the literature are shown below.

* M V Kulkarni et al\textsuperscript{113} have synthesized an array of angularly fused polycyclic heterocycles with coumarin, benzofuran and pyridine rings from 4-bromomethylcoumarins and salicylonitrile as shown below.

\[
\text{Synthesis of } 5H\text{-coumarin}|4,3-c|\text{pyridin-5-ones derivatives were carried out by K E Litinas and D N Nicolaides et al}^\text{114} \text{ by reacting O-methyl-4-coumarin carbaldehyde oxime as an azadiene with electron-deficient and electron rich dienophiles, via one-step hetero Diels–Alder cycloaddition reactions.}
\]

\[
\text{Synthesis of 3-substituted-2,5-dioxo-pyrano}[3,2-c|\text{benzopyrans were carried out by V V Mulwad et al}^\text{115} \text{ by reacting 4-hydroxy-3-formyl}
\]


\[
\text{O} \quad \text{O} \\
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{OCH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array}
\]

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
\begin{array}{c}
\text{N} \\
\text{R}_1 \\
\text{R}_2
\end{array}
\]
coumarin with N-acetyl glycine or N-benzoyl glycine in the presence of acetic acid in refluxing ethanol.

\[
\begin{align*}
\text{O} & \quad \text{CHO} \quad R-NH-CH_{2}-COOH \\
\text{OH} & \quad \text{AcOH, EtOH} \quad \to \quad \text{O} \\
\end{align*}
\]

\[C \ A \ Kontogiorgis \ et \ al^{16}\] have synthesized anti-inflammatory active 3-methyl-3,4,4a,10a-tetrahydro-2H-1,5-dioxa-3-aza-phenanthren-6-one by reacting 7-hydroxy coumarin with formaldehyde and methyl amine.

\[
\text{HO} \quad \text{O} \quad \text{CHO} \quad \text{HCHO} \quad \text{CH}_{2}\text{NH}_{2} \quad \to \quad \text{N} \quad \text{O} \\
\]

\[Jie \ Wu \ et \ al^{17}\] have synthesized quinolino[3,2-c]coumarins by the reaction of an appropriate 3-formyl-4-chlorocoumarin and aryl isocynide in the presence of perchloric acid.

\[
\begin{align*}
\text{Cl} & \quad \text{CHO} \quad \text{NC} \quad 10\% \text{HClO}_4 \quad \text{MeOH} \quad \to \quad \text{N} \\
R & \quad \text{R} \quad \text{R} = \text{CH}_{3}, \text{F}, \text{Cl} \quad R = \text{COCH}_{3}, \text{NET}_{2}, \text{Cl} \\
\end{align*}
\]

\[F \ Lubomir \ et \ al^{18}\] have prepared various 1,4-benzodiazepines by reacting 4-azido-3-coumarincarboxaldehyde with aromatic diamine.

\[
\begin{align*}
\text{N}_3 & \quad \text{CHO} \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \quad \to \quad \text{N} \\
\text{O} & \quad \text{CHO} \\
\end{align*}
\]
Regioselective synthesis of coumarin annulated poly-heterocycles by [3,3] sigmatropic rearrangement has been reported by K C Majumdar\(^{19}\) by reacting 4-hydroxy coumarin with 1-aryloxy-4-chlorobut-2-yne.

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \\
\text{R} & \quad \text{Ph}
\end{align*}
\]

\(\xrightarrow{(i) \text{ dry Me₂CO, NaI}} \)

\(\xrightarrow{(ii) \text{ chlorobenzene, reflux}} \)

\(\xrightarrow{(iii) \text{ anhy. AlCl₃, dry DCM; r.t., 0.5 h.}} \)

\[
\text{O} \quad \text{O} \\
\text{R} \quad \text{O}
\]

1.7 Naturally occurring coumarins

Coumarins occur naturally in plants and microorganisms. Approximately 1000 coumarin derivatives have been isolated from over 800 species of plants and microorganisms\(^{120}\). Most of them are found in plants with four major families, the Umbelliferae, Rutacea, Leguminosae and Compositae, the other come from animals or microorganisms. Some of the important naturally occurring coumarins are shown below.
1.8 Medicinal and industrial applications of coumarins

Coumarin and its derivatives have attracted considerable interest because of their various physiological and biochemical properties. P K Bose\textsuperscript{130} has reviewed the biochemical properties of natural coumarins. Coumarin itself inhibits the germination and subsequent root growth of plants. W Sigmund \textsuperscript{131} noted the effect of both daphnetin and its isomer aesculetin, on seed germination. There is also good probability that coumarins act as growth regulators in number of plants\textsuperscript{132}. Some of the medicinally important coumarins are shown below.
Coumarins have interesting cytogenetic properties\textsuperscript{133}. \textit{E Quercioli}\textsuperscript{134} has studied cytohistological and macroscopical effects of coumarin and its derivatives.

\textit{K P Link et al}\textsuperscript{135} isolated a hemorrhagic agent from the spoiled sweet clover which was found to be 3,3-methylene bis(4-hydroxy coumarin). This led to the preparation and testing of several other 4-hydroxy coumarin derivatives as anticoagulant drugs and number of very effective drugs of this group, such as warfarin sodium, tromexan, coumachlor and marcoumar are in the market. Later on, \textit{R B Arora} and \textit{C N Mathur}\textsuperscript{136} found that weak anticoagulant activity was shown by 3- and 4-phenyl coumarins and marked activity by one of the later namely calophyllolide. 4-Phenyl coumarin derivatives isolated from \textit{H. standleyana} and \textit{H. latiflora} are effective as hypoglycemic agents in diabetic condition\textsuperscript{137}.

Khellactone coumarins are notable because of their bioactivities, including anti-HIV, antitumour\textsuperscript{138} and anti-platelet aggregation\textsuperscript{139}. One member of this family, Suksdorfin is a dihydroseselin type angular pyranocoumarin.

A furanocoumarin, Imperatorin obtained from methanolic extracts of dried roots of \textit{Ferula sumbul} showed an HIV inhibitory activity\textsuperscript{140}. Imperatorin also induces vasodialation\textsuperscript{141} via inhibiting voltage dependant Ca channels and receptors mediated Ca\textsuperscript{2+} influx and release.

\textit{K H Lee et al}\textsuperscript{42} isolated Neo transchinlactone, a furano coumarin derivative from the EtOH extract of \textit{S. miltiorrhiza}. It was evaluated \textit{in vitro} against several human cancer cell lines. It showed significant inhibition against two ER+ human breast cancer cell lines. Another novel furanocoumarin derivative, 8-benzoyl-4,9-dimethyl angelicin was identified by \textit{H P Hsieh et al}\textsuperscript{43} to inhibit influenza A (H1N1) virus induced cytopathic effect in Madin-Darby canine kidney cell culture and act as an anti influenza agent by inhibiting ribonucleoprotein complex associated activity.
Sesquiterpene coumarin ethers\textsuperscript{144} viz. (1) Microlobidene, (2) Farnesiferol C, (3) Galbanic acid and (4) Kellerin, inhibits the human rhinovirus (HRV) coat protein and are also promising candidates to treat and prevent a number of upper respiratory disease.

Novobiocin is a natural product isolated from soil samples containing Streptomyces spheroids\textsuperscript{145} and has clinical use for the treatment of bacterial infection\textsuperscript{146,147} and more recently some forms of cancer\textsuperscript{148}. Neckers and coworkers proposed that novobiocin also possess anti-tumor activity\textsuperscript{149}. S G Tsodikova et al\textsuperscript{150} reported that amino coumarin antibiotics clorobiocin and coumermycin A1, along with novobiocin are highly potent inhibitors of the bacterial type 2 topoisomerase DNA gyrase.

Coumarleucasin was isolated from the acetone extracts of the roots of \textit{Leucas inflate} and Calophyllolide was isolated from the alcoholic extracts of the nuts of \textit{Calophyllum inophyllum}. Both are reported to have a potent anti-inflammatory properties\textsuperscript{151,152}.

Coumarleucasin was isolated from the acetone extracts of the roots of \textit{Leucas inflate} and Calophyllolide was isolated from the alcoholic extracts of the nuts of \textit{Calophyllum inophyllum}. Both are reported to have a potent anti-inflammatory properties\textsuperscript{151,152}.

The aerial parts of \textit{Heterotheca inuloides} plant is used in folk medicine for the topical treatment of skin wounds and injuries\textsuperscript{153}. 7-(3,3-Dimethylallyloxy)coumarin was found as one of the components of the extract of the aerial parts of this plant.
Recently, S C Ghosh et al\textsuperscript{154} proposed that coumarin derivatives of \textit{N,N-dimethylsphingosine} (DMSP) were apparently biologically equivalent to DMSP in terms of tumor cell cytotoxicity.

\textit{R C Elderfield} and \textit{J Roy}\textsuperscript{155} have synthesized nitrogen mustards from 6-substituted coumarins as potential anticancer agents. Coumarin itself has been reported to be a moderately potent inhibitor of chemical carcinogen induced neoplasia\textsuperscript{156}. \textit{A Lacy et al}\textsuperscript{157} have reported some coumarin derivatives with anti-cancer activity. \textit{P K Murthy et al}\textsuperscript{158} have reported coumarin derivatives with anti filarial activity. \textit{N Hamdi et al}\textsuperscript{159} have reported antioxidant and anti bacterial activity of coumarin derivatives. \textit{W.F. Smyth et al}\textsuperscript{160} have shown anti microbial activity of naturally occurring and synthetic coumarin derivatives.

\textit{V Lanzotti et al}\textsuperscript{161} isolated a new prenylated coumarin, Pavetin from leaves of an \textit{Aesculus Pavia} genotype. It displays a significant anti fungal activity.

An isoprenylated dihydroxy coumarin, Mammea E/BB was found to inhibit both hypoxia induced and iron chelator induced hypoxia inducible factor-1 activation in human breast tumor (T47D) cells. It also suppresses the hypoxia induction of secreted VEGF protein (T47D cells) and inhibited cell vialibity/proliferation in human tumor cell lines and human breast tumor cell migration\textsuperscript{162}.

Certain pyrano fused coumarins are reported to have antimicrobial activity\textsuperscript{163}. Some pyranocoumarins are identified to embody a novel and unique pharmacophore antituberculosis activity\textsuperscript{164}. Pyranocoumarins derivatives, (+) Inophyllum B and (+) Calanolide A are found to be anti HIV inhibitors\textsuperscript{165}.

Certain amino and acetyl amino coumarins are reported to have antioxidant activity\textsuperscript{166}. \textit{B Refouvelet et al}\textsuperscript{167} have reported some coumarin derivatives which protect liver cells from damage by peroxides.

\textit{R A Kusanur et al}\textsuperscript{168} have reported certain indole and diazipine coumarin derivatives which are having antimicrobial and antianxiety activity.
Although simple coumarin has a very low fluorescence quantum yield, many natural coumarins and synthetic derivatives are highly fluorescent and have high quantum yields. The synthetic coumarins have been used extensively as fluorescent brightening agents in detergents, paper and textiles to mask yellowing in white materials. Various coumarin derivatives have been used as dyes in laser technology\textsuperscript{169} and as fluorescent indicator\textsuperscript{170}. 7-(2'-Benzoazolyl)-3-phenyl coumarin\textsuperscript{171} and 2-(3'-coumarinyl) benzoazoles\textsuperscript{172} have been reported to be optical brighteners for polyesters, polyamides and polyvinylchlorides. 2-(3'-Coumarinyl)-naphthoxazoles with dialkylamine substituents in 7\textsuperscript{th} position of coumarin ring exhibit brilliant fluorescence with absorption in visible range and are useful for dyeing of organic fibers\textsuperscript{173}. A novel application of coumarin fluorescence is in the field of tunable laser dyes\textsuperscript{174}. Y D Reddy\textsuperscript{175} and other have reported synthesis of 3-heteroaryl coumarins as optical brighteners. 3-(2-Benzimidazoyl)-7-(diethyl amino) coumarins\textsuperscript{176} are reported as dyes. Several coumarins containing heterocyclic moieties such as thiadiazole, oxadizole, 1,2,3-triazole are reported to have fluorescent brightening properties\textsuperscript{177-179}. A M Asiri\textsuperscript{180} have reported novel biscoumarins having an ester group in position 4, possess good UV absorption properties.

Certain metal complexes of coumarin are also reported to have various medicinal and industrial applications. I Kostova \textit{et al}\textsuperscript{181} have reported lanthanide complexes of 4-methyl-7-hydroxycoumarin. These complexes have been reported for their good cytotoxic activity against transformed leukemic cell lines (P3HR1 & THP-1). I Manolov \textit{et al}\textsuperscript{182} have reported cytotoxic screening of new complexes of cerium, lanthanum and neodymium with nifcoumar (4-hydroxy-3-[1-(4-nitrophenyl)-3-oxobutyl]-coumarin) sodium salt. S-G Roh \textit{et al}\textsuperscript{183} have reported luminescent lanthanide complexes based on coumarin-3-carboxilic acid for advanced photonic application such as planar waveguide amplifier and light emitting diodes.
1.9 Summary of the present work

A survey of the literature reveals that number of coumarin derivatives having heterocyclic moieties either as substituent groups or fused with parent coumarin nucleus possess variety of functions and are widely used in drugs and dyes. Because of this wide utility, the synthesis of coumarin has remained a subject of an active interest. Looking to the importance of these hetero coumarins and with a view to exploring new methods of their synthesis, the present work was undertaken.

In Chapter 2, synthesis of various bipyridinyl coumarins have been carried out. The synthesis of various 3-(4-aryl-2,3′-bipyridin-6-yl)coumarins and 3-(4-aryl-2,4′-bipyridin-6-yl)coumarins have been carried out by the reaction of appropriate 3-(ω-bromoacetyl) coumarin pyridinium salt with 3-aryl-1-(pyridin-3-yl)prop-2-en-1-one and 3-aryl-1-(pyridin-4-yl)prop-2-en-1-one (chalones) in the presence of ammonium acetate in refluxing glacial acetic acid. The formation of pyridine nucleus follows Krohnke’s mechanism. The required chalcones were prepared by the reaction of appropriate 3-acetyl pyridine and 4-acetyl pyridine with various aromatic aldehydes in the presence of sodium hydroxide in ethanol.

The work presented in Chapter 3 is distributed in two sections. The section 1 of this chapter deals with the synthesis of various pyrido/quino fused and pyridyl/quinolinyl carbonyl substituted coumarins. The synthesis of various 8H-9,10-dihydrocoumarino[4,3-b]cyclopenta[e]pyridines; 8,9,10,11-tetrahydrocoumarino[4,3-b]quinolines; 8H-coumarino[4,3-b]indenol[2,1-e]pyridines and 8,9-dihydro benzo[h]coumarino[4,3-b]quinolines have been carried out by reacting appropriate 4-hydroxy coumarins with Mannich bases of cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively in the presence of ammonium acetate in refluxing acetic acid. The formation of pyridine nucleus follows Krohnke’s mechanism. The required Mannich bases of cyclopentanone, cyclohexanone, 1-indanone and α-tetralone were prepared by reacting cyclopentanone, cyclohexanone, 1-indanone and α-tetralone with dimethyl amine and formaldehyde in ethanol. In addition to above synthesized compounds,
8-(6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonyl)-7-hydroxy-4-methylcoumarin, 7-hydroxy-4-methyl-8-(5,6,7,8-tetrahydroquinoline-3-carbonyl)coumarin, 7-hydroxy-8-(5H-indeno[1,2-b]pyridine-3-carbonyl)-4-methylcoumarin and 8-(5,6-dihydrobenzo[h]quinoline-3-carbonyl)-7-hydroxy-4-methylcoumarin have also been synthesized by reacting 4-methyl-7-oxa-10-oxo-benzo[h]coumarin-9-carbaldehyde with cyclopentanone, cyclohexanone, 1-indanone and α-tetralone respectively in the presence of ammonium acetate in refluxing glacial acetic acid. Here also, the formation of pyridine nucleus follows Krohnke’s mechanism. The section 2 of this chapter deals with the synthesis of various coumarinyl substituted pyrido fused coumarins. The synthesis of various 2-(coumarin-3-yl)-coumarino[4,3-b]pyridines have been carried out by reacting various 4-chloro-3-formyl coumarins with appropriate 3-(ω-bromoacetyl) coumarin pyridinium salt in the presence of ammonium acetate in refluxing glacial acetic acid. Here too, the formation of pyridine nucleus follows Krohnke’s mechanism.

In Chapter 4, synthesis of various pyridyl substituted benzo[c]coumarins have been carried out. The synthesis of various 7-hydroxy-9-pyridinyl benzo[c]coumarins has been carried out by reacting appropriate 3-(ω-bromoacetyl) coumarin pyridinium salt with appropriate acetyl pyridines in the presence of sodium acetate in glacial acetic acid.

The work presented in Chapter 5 deals with microwave assisted synthesis of various quinolinyl-pyrazolyl substituted coumarins. Various 3-(1-acetyl-5-(2-hydroxy/aryloxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-3-yl)coumarins and 3-(5-(2-hydroxy/aryloxyquinolin-3-yl)-1-propionyl-4,5-dihydro-1H-pyrazol-3-yl)coumarins have been synthesized by reacting various 3-(3-(2-hydroxy/aryloxyquinolin-3-yl)acryloyl)coumarins (coumarin chalcones) with hydrazine hydrate in acetic/propionic acid under microwave irradiation. Various 1-aryl-3-(5-(2-hydroxy/aryloxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-3-yl)coumarins have been synthesized by reacting various 3-(3-(2-hydroxy/aryloxyquinolin-3-yl)acryloyl)coumarins (coumarin chalcones) with
appropriate phenylhydrazine using acetic acid as solvent under microwave irradiation.

All the compounds synthesized in chapter 2, 3, 4 and 5 have been characterized by analytical and spectral data.

The Chapter 6 comprises basic introduction of antimicrobial activities and the results of antimicrobial efficiency of all the synthesized compounds. The antibacterial activity (Minimum Inhibition Concentration) of the synthesized compounds has been screened against Gram negative bacteria viz. E. coli and S. typhi, Gram positive bacteria viz. S. aureus and B. subtillis and against fungi viz. C. albicans and A. niger. The in vitro antimicrobial activity of all the synthesized compounds was carried out by Broth micro dilution method\textsuperscript{184}. 

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