CHAPTER 1

Introduction to chromene derivatives and their applications

Chromene (Benzopyran) is one of the privileged medicinal pharmacophore which appears as an important structural component in natural products and generated great attention because of their interesting biological activities.

Coumarin belongs to a group of benzopyrones, which consists of a benzene ring joined to a pyrone nucleus. Benzo-α-pyrones (2H-chromen-2-one) commonly known as coumarin, are reported to possess a wide range of biological activities [1-2].Coumarin (2H-chromen-2-one) and its derivatives are widely distributed in nature [3]. They are regarded as a promising class of bioactive heterocyclic compounds that exhibit wide range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer, anti-oxidant, anti-convulsant, anti-inflammatory and anti-hypertensive activities etc [4].

In particular, their physiological, bacteriostatic and anti-tumor activities make these compounds attractive backbone for derivatization and screening as novel therapeutic agents. Recently coumarin derivatives have been explored in the field of fluorescence materials and laser dyes [5], nonlinear optical materials [6], photorefractive materials [7].

α,β-Unsaturated ketones, commonly known as chalcones are important class of natural as well as synthetic products which show variety of biological activities. During last few decades, chalcone derivatives have been reported having potent anticancer activity with low side effects and better solubility for therapeutic applications [8-9].

Simple structural modification in chalcone moiety with heterocycles, polyarene compounds or organometal complexes may lead to new anticancer agents with promising activity [10-11]. Chalcone derivatives are also known for their excellent blue light transmittance, good crystallisability [12] and photosensitivity [13]. Photosensitive polymers containing chalcone derivatives have been studied for photoalignment film [14–15].

Cancer is one of the dreadful diseases after cardiovascular diseases all over the world. Most of the cancers are defined by uncontrolled growth of cells without differentiation due to the deregulation of essential enzymes and other proteins controlling cell division and proliferation [16-17]. Out of many therapeutic strategies, chemotherapy shows significant clinical responses. At the same time, these chemotherapeutic agents have a small therapeutic window

Summary

with non-specificity and high-systemic toxicity. To get selective chemotherapeutics with very low side effects is a major challenge in treatment of cancer [18].

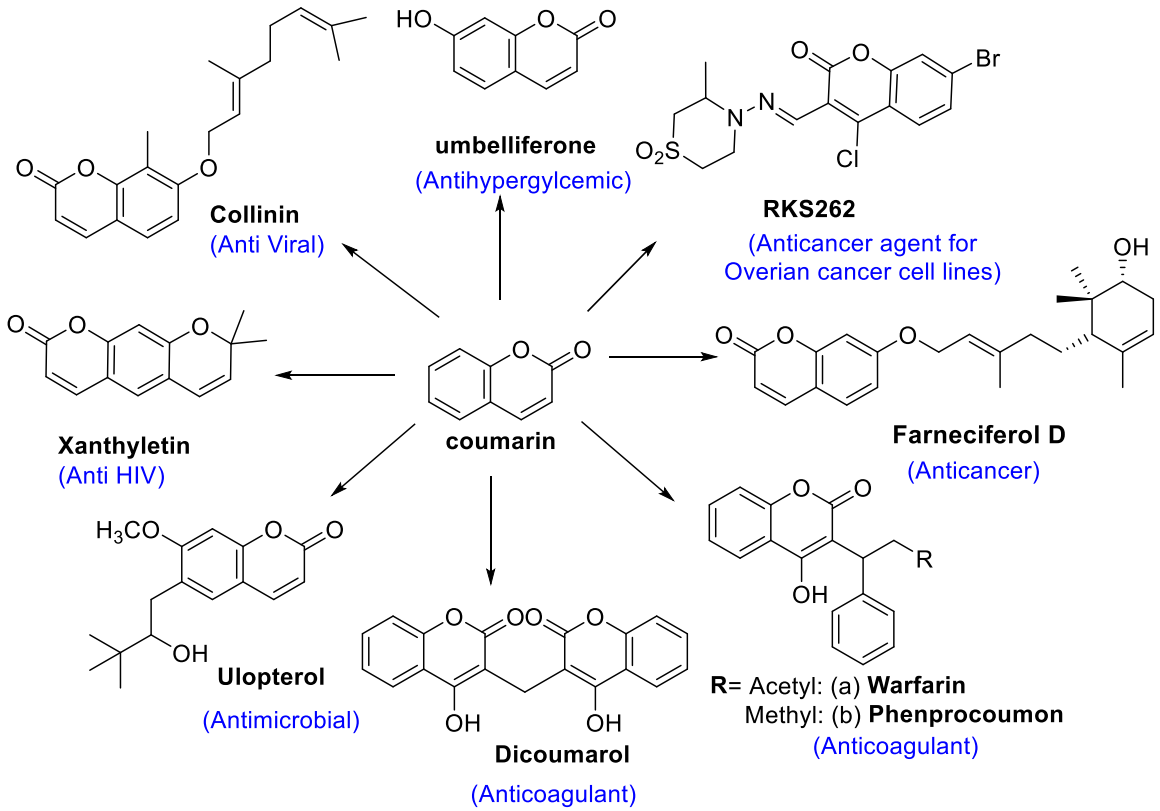


Figure 1: Some biologically active Chromene-2-one derivatives

In coumarin compounds, the studied properties are fluorescence, colouring agents, liquid crystalline and gelation behaviour in water and organic solvents. These properties received special attention because they are considered as promising candidates for the next generation of materials, due to their dynamic response, environmental compatibility and low energy processing with non-covalent interactions to form organized soft materials [19].

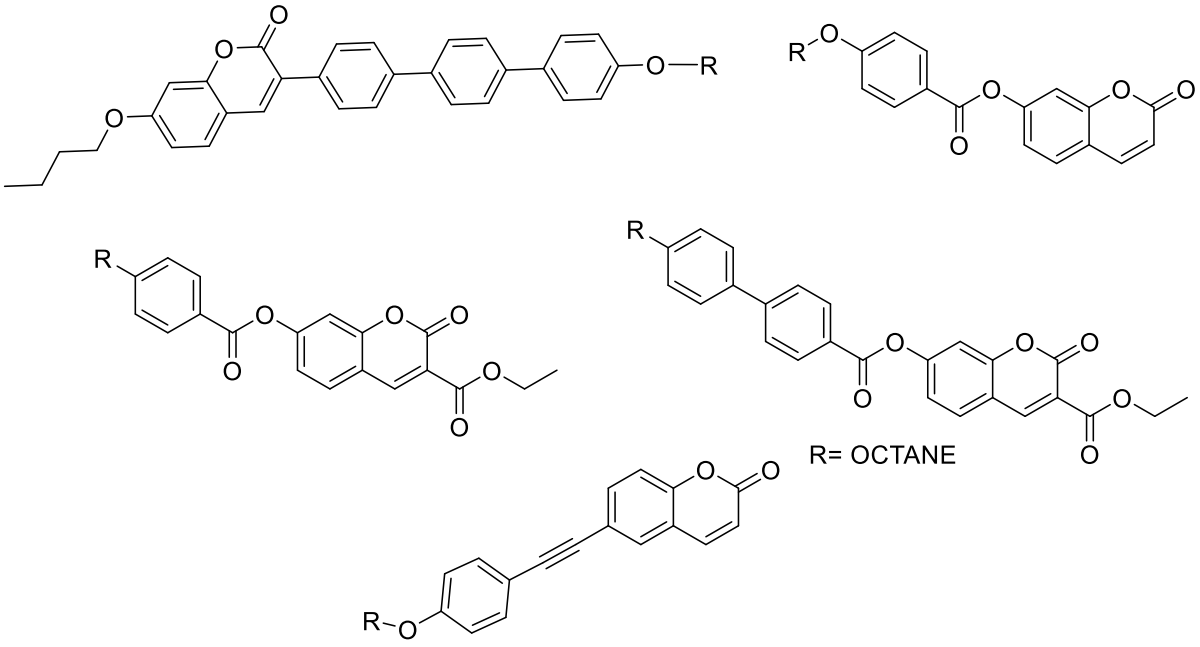


Figure-2: Chromen-2-one derivatives with liquid crystalline properties

Various coumarin derivatives showing mesomorphic state are reported (**Figure-2**). Ethyl 7-hydroxycoumarin-3-carboxylate derivatives showed excellent liquid crystal behavior majorly Smectic-A and nematic phase [20].

CHAPTER 2

Synthesis and applications of 3,7-disubstituted chromen-2-one derivatives as anticancer agent

Chapter 2 is divided into two series, in series-1 synthesis of 3-acetyl 7-hydroxy chromen-2-one is carried out and then various amide derivatives of it were synthesized. In 2nd series, 3-carboxylate 7-hydroxy chromen-2-one was prepared and then its various amide derivatives were synthesized. All the compounds were characterized by using different spectral techniques like ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and C,H,N analysis

Compounds were screened for their anticancer activity by using MTT assay method in lungs (A549) and breast cancer (MCF7) cell lines. Compound **1b** showed excellent anticancer activity against A549 cell line with IC_{50} 0.16 nM. Compound **1b** and **1e** were studied further for its binding with CT-DNA by UV and Fluorescence spectroscopy

Scheme-1

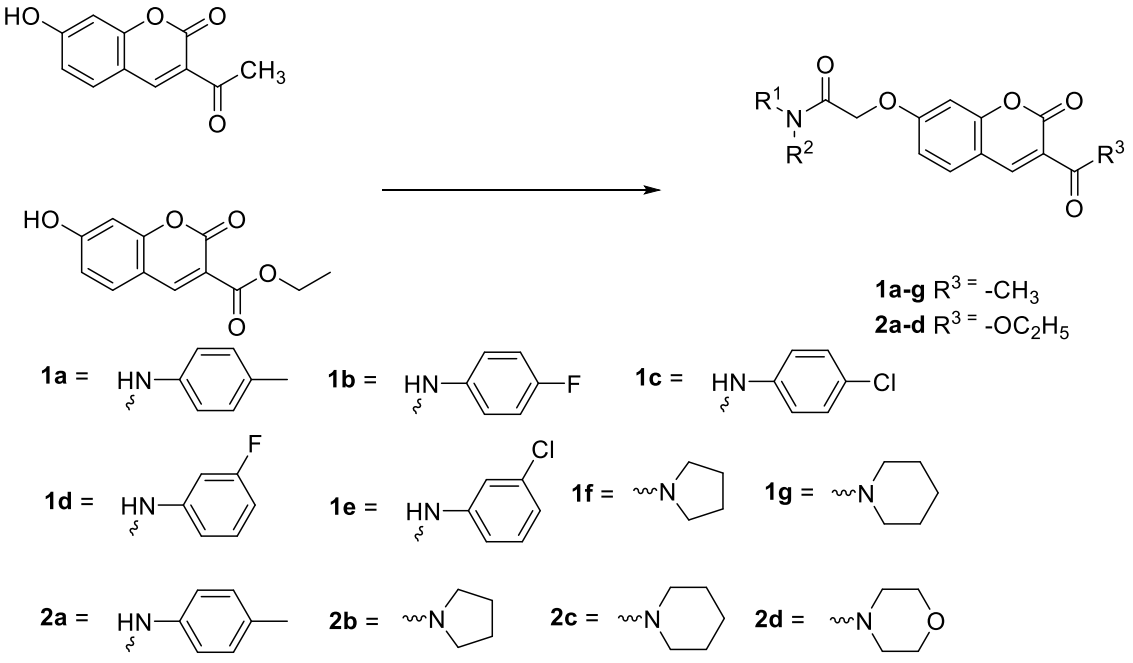


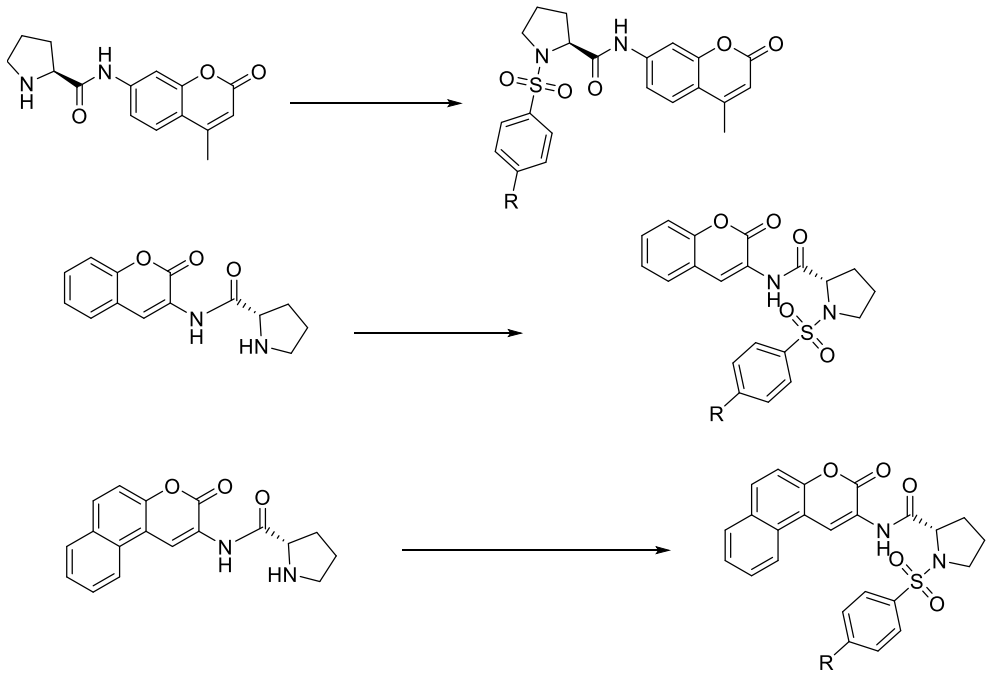
Figure-1: chromen-2-one derivatives as anticancer agents

CHAPTER 3

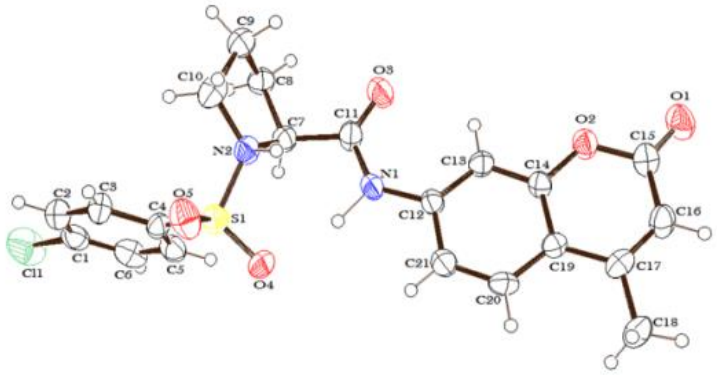
3A: Synthesis of proline-sulphonamide derivatives of chromen-2-ones as anticancer and antidiabetic agents

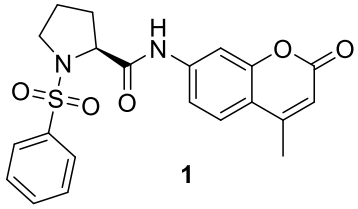
Chapter 3A deals with preparation of proline sulphonamide hybrid derivatives of 7-amino-4-methyl-2H-chromen-2-one, 3-amino-2H-chromen-2-one and 2-amino-3H-benzo[f]chromen-3-one**.** All the intermediates and final compounds were characterized by using different spectral techniques like ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and C,H,N analysis for all compounds.

The anticancer activity of **1** to **9** was studied by MTT assay in lungs and breast cancer cell line and antidiabetic activity by DPP-4 inhibition assay.



Single crystal of compound **3** was obtained which conformed formation of compound


C9
C10
C8
O3
C11
C7
N2
N1
O2
O1
C15
C13
C14
C16
C12
C21
C19
C17
C20
C18
S1
O4
O5
C4
C3
C2
C1
C6
C5
Cl1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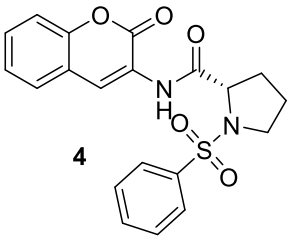
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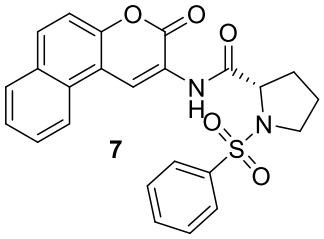
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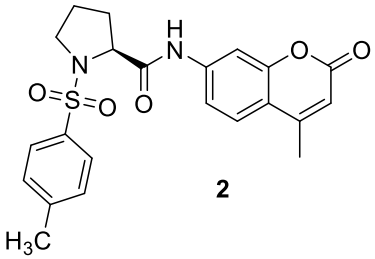
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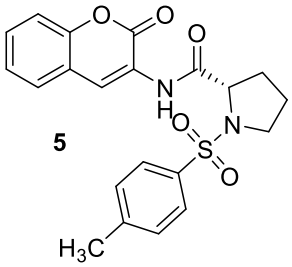
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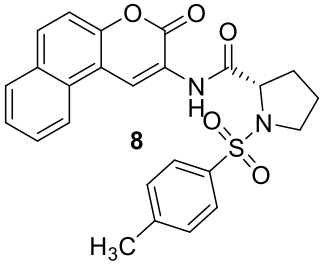
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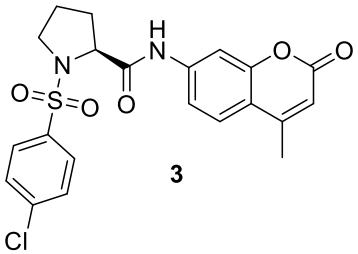
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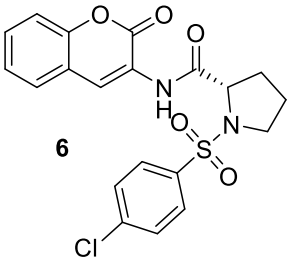
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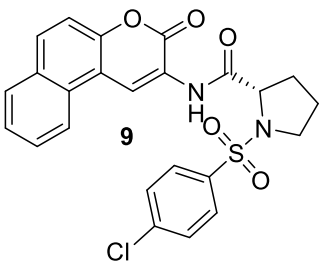

9

3B: Synthesis and Cytotoxic studies of Chalcone derivatives of chromen-2-ones and 3-Aminomethyl pyridine

7-amino 4-methyl chromen-2-one and 3-amino chromen-2-one, on reaction with bromoacetyl bromide followed by 3-amino methylpyridine gave compound **1** and **2** as shown in **Figure-1**

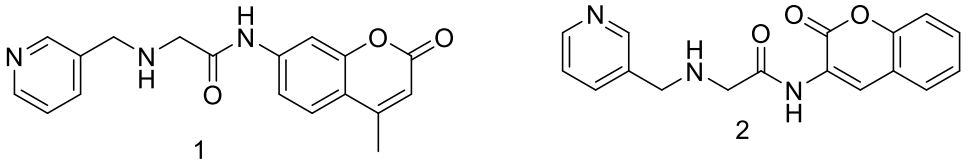
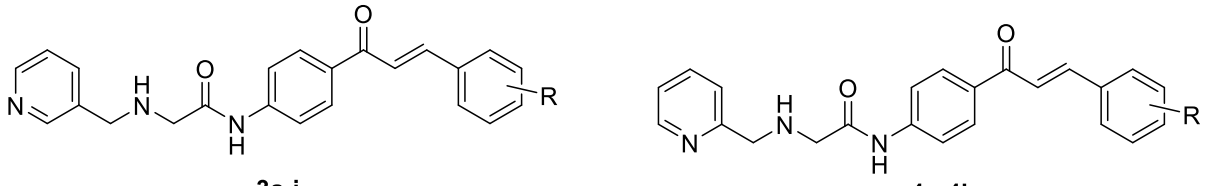


Figure-1 Chromen-2-one derivatives for anticancer activity

p-Amino acetophenone on reaction with various aldehydes in the presence of base gave chalcone which on reaction with bromoacetyl bromide followed by 3-aminomethyl pyridine gave compounds **3a-j** and 2-methylaminopyridine gave compounds **4g, 4i** as shown in **Figure-2** All newly synthesized compounds were characterized by using different spectral techniques like ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and elemental analysis. Compounds **3g** and **3i** gave excellent anticancer activity by MTT assay in lung and breast cancer cell lines. Both compounds **3g**, **3i** showed good binding constant Kb. LDH and EtBr/AO assay confirmed cell death by apoptosis pathway.



3a-j

a, R = H
b, R =4-Me
c, R =4-OCH_3
d, R =4-F
e, R =4-Cl
f, R =4-NO_2
g, R =3-OCH_3
h, R =2-Cl
i, R =3-Cl
j, R =2,4-Cl

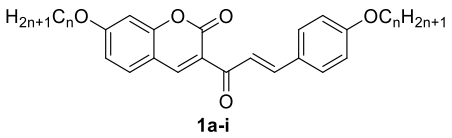
4g,4i

Figure-2 Various chalcone derivatives for anticancer activity

CHAPTER 4

4A: Synthesis of chalcone derivatives of chromen-2-ones with mesogenic properties

This chapter deals with synthesis of chalcone derivatives. 7-hydroxy-3-acetyl chromen-2-one on reaction with p-hydroxy benzaldehyde gave chalcone. The free hydroxyl group at 7th position of coumarin and 4th position of benzene ring was further alkylated with different alkyl halides to give compounds **1a-i**. All newly synthesized compounds **1a-i** were characterized by using different spectral techniques like ^{1}H NMR, ^{13}C NMR, IR, ESI-MS and elemental analysis, Transition temperatures for all compounds were recorded by Differential Scanning Calorimetry (DSC). Liquid crystalline phase study of all synthesized compounds was studied by Polarizing Optical Microscope (POM). Compounds showed mesogenic properties such as nematic and smectic phase

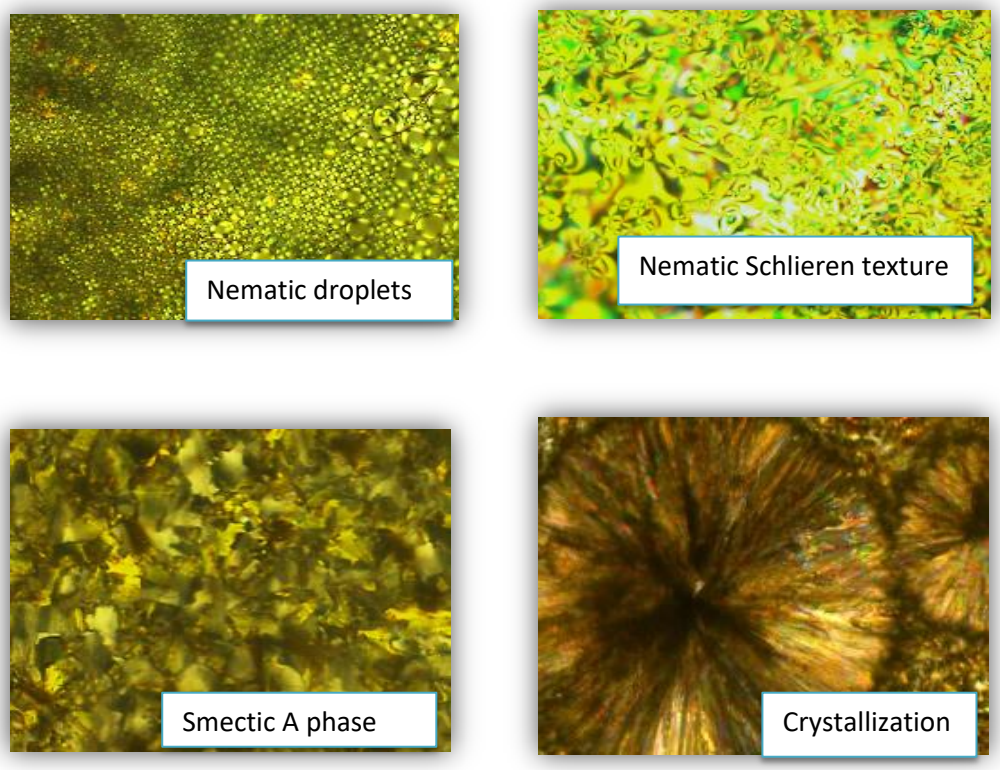


1a-i

n = 2, 4, 6, 8, 10, 12, 14, 16, 18

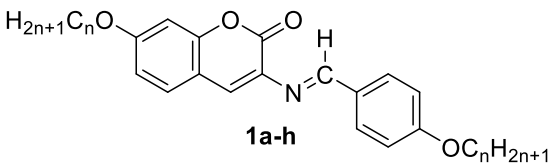
Figure-1 Chromen-2-one chalcone derivatives studied of liquid crystalline property

Figure-2: Polarizing optical microscope images on cooling cycle of Chalcones **1d**



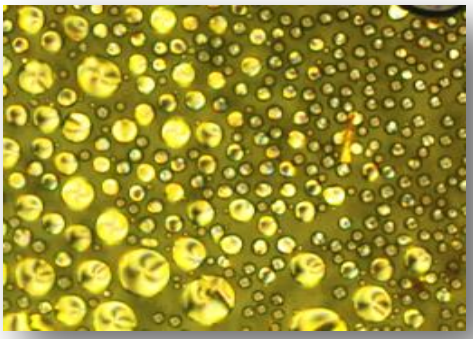
4B: Synthesis of Schiff base derivatives of chromen-2-ones with mesogenic properties

3-Amino 7-hydroxy chromen-2-one on reaction with various alkyl halides in presence of base like K_2CO_3 gave 7-alkoxy-3-amino chromen-2-one. p-Hydroxy benzaldehyde on reaction with various alkyl halides gave 4-alkoxy benzaldehydes which on reaction with various 7-alkoxy-3-amino chromen-2-one in presence of catalytic amount of acetic acid gave schiff bases 1**a-k** as shown in Figure-1. These new imine derivatives 1**a-k** were characterized by various spectral techniques like ^{1}H MNR, ^{13}C NMR, IR, ESI-MS and elemental analysis, DSC studies were carried out and the mesogenic properties were also studied using Polarizing Optical Microscope and Differential Scanning Calorimetry. The compound showed various phase such as nematic and smectic as shown in **Figure-2**

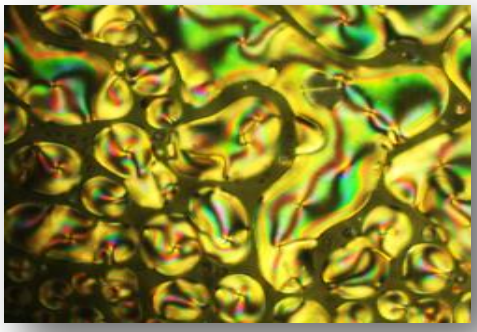


n = 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18

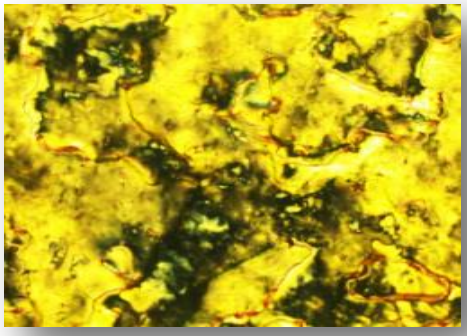
Figure-2: Polarizing Optical Microscope images on cooling cycle cycle of Imine **1f**.



Nematic droplets



Nematic Schlieren texture

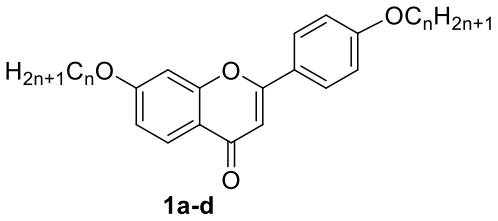


Nematic marble

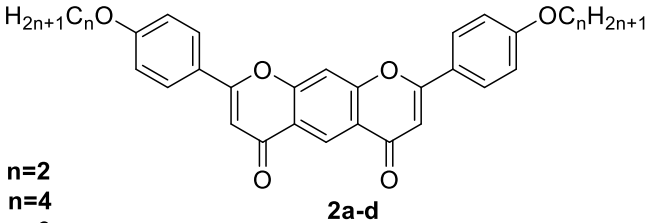
Smectic A phase

CHAPTER-5: Synthesis of chromen-4-one and bis-chromen-4-one derivatives and its applications

2,4-Dihydroxy acetophenone on reaction with p-hydroxy benzaldehyde in presence of base like pyrrolidine gave dihydroflavone which was dehydrogenated in presence of I_2, DMSO to give flavone **1**. The free hydroxyl groups in compound were alkylated using various alkyl halides in presence of base like K_2CO_3 to give desired flavones **1a-d**. Similarly bis flavones were synthesized by starting with 2,4-dihydroxy-1,5-diacetyl benzene, The structures of all the newly synthesized compounds were confirmed by various spectral techniques like ^1H NMR, ^{13}C NMR, IR, ESI-MS. The mesogenic properties of these compounds were studied using polarizing optical microscope, but unfortunately not a single compound showed liquid crystalline property.



1a-d



2a-d

a: n=2
b: n=4
c: n=6
d: n=8

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