Synopsis

of

The Thesis Entitled

Synthesis and Applications of Oxygen/Nitrogen Containing Five/Six Membered Heterocyclic Compounds

To be submitted to M. S. University of Baroda

For the Degree

Of

DOCTOR OF PHILOSOPHY

In Chemistry

By

Ms. Jayashree V Patil

Under guidance of

Prof. Shubhangi S. Soman

Department of Chemistry,

Faculty of Science,

The M. S. University of Baroda

Vadodara- 390 002 (India)

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Synopsis

To be submitted to The Maharaja Sayajirao University of Baroda

For the degree of **DOCTOR OF PHILOSOPHY**

Name of the student **:** Jayashree Vishvasrao Patil

Faculty **:** Science

Subject **:** Chemistry

Name of Guide **:** Dr. Shubhangi S. Soman (M.Sc. PhD)

Title of the Thesis **:** Synthesis and Applications of Oxygen/Nitrogen Containing Five/Six Membered Heterocyclic Compounds.

Registration Number **:** FOS/2271

Date of Registration **:** 16-02-2021

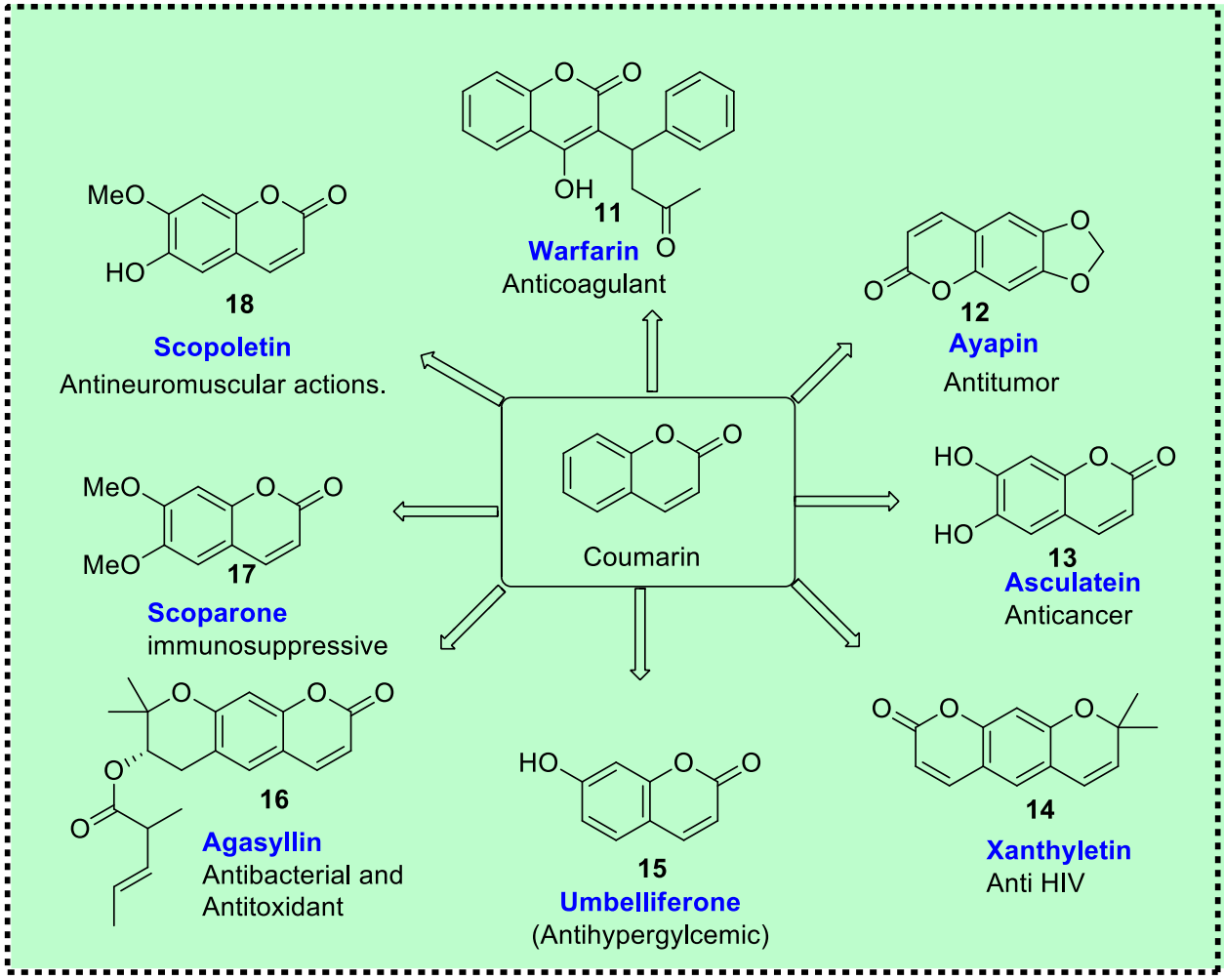
Place of Work **:** Department of Chemistry, Faculty of Science,
The M. S. University of Baroda
Vadodara
(Gujarat, India)

Contents of Thesis

Contents of Executive Summary

Chapter-1: Introduction to benzopyran derivatives and their applications

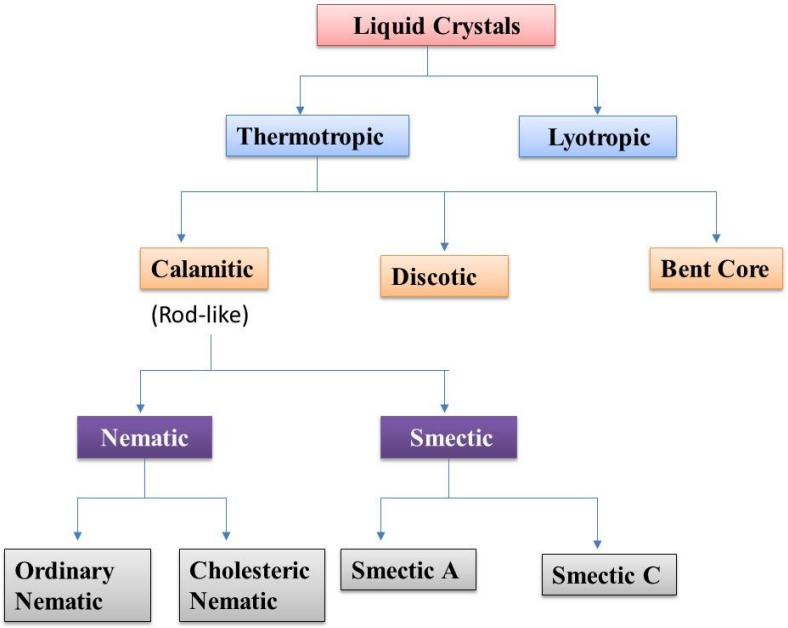
Coumarin- (2H-chromen-2-one) is an oxygen containing heterocyclic organic compound in the benzopyrone chemical class, which is a colourless crystalline substance in standard state. It is found naturally in many plants families having fragrance. Coumarin was first isolated by Vogel in 1820 from Tonka beans. Coumarins belong to the benzopyrone family commonly found in many medicinal plants. Natural coumarins demonstrated a wide spectrum of pharmacological activities, including anti-inflammatory, anticoagulant, anticancer, antibacterial, antimalarial, antifungal, antiviral, Alzheimer's disease inhibition, neuroprotective, anticonvulsant, phytoalexins, ulcerogenic, and antihypertensive. There are very few studies on the bioavailability of coumarins On the evidence of varied pharmacological properties, the present work presents an overall review of the derivation, availability, and biological capacities of coumarins with further consideration of the essential mode of their therapeutic actions. In conclusion, a wide variety of coumarins are available, and their pharmacological activities are of current interest thanks to their synthetic accessibility and riches in medicinal plants. Coumarins perform the valuable function as therapeutic agents in a range of medical fields.



Apart from this biological applications coumarins have been used in a wide range of applications, such as dye-sensitised solar cells, laser dyes and optical sensors. Coumarin derivatives have been explored in field of fluorescence materials, laser dyes, nonlinear optical materials, photorefractive materials. 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.

Mesogenic Behaviour of Coumarin –

Liquid Crystal- Liquid crystal is a delicate state of matter that exist between crystalline solid and amorphous liquids.



Most liquid crystals are thermotropic; their degree of orientational and positional order depends on temperature and so their liquid crystalline phase occurs within a limited temperature range between the solid and liquid phase. Calamitic liquid crystals are characterized by their elongated, rod-like shape, and composed of three main structural elements: rigid ring systems, connective linkage groups, and flexible terminal groups.

Objectives of Work:

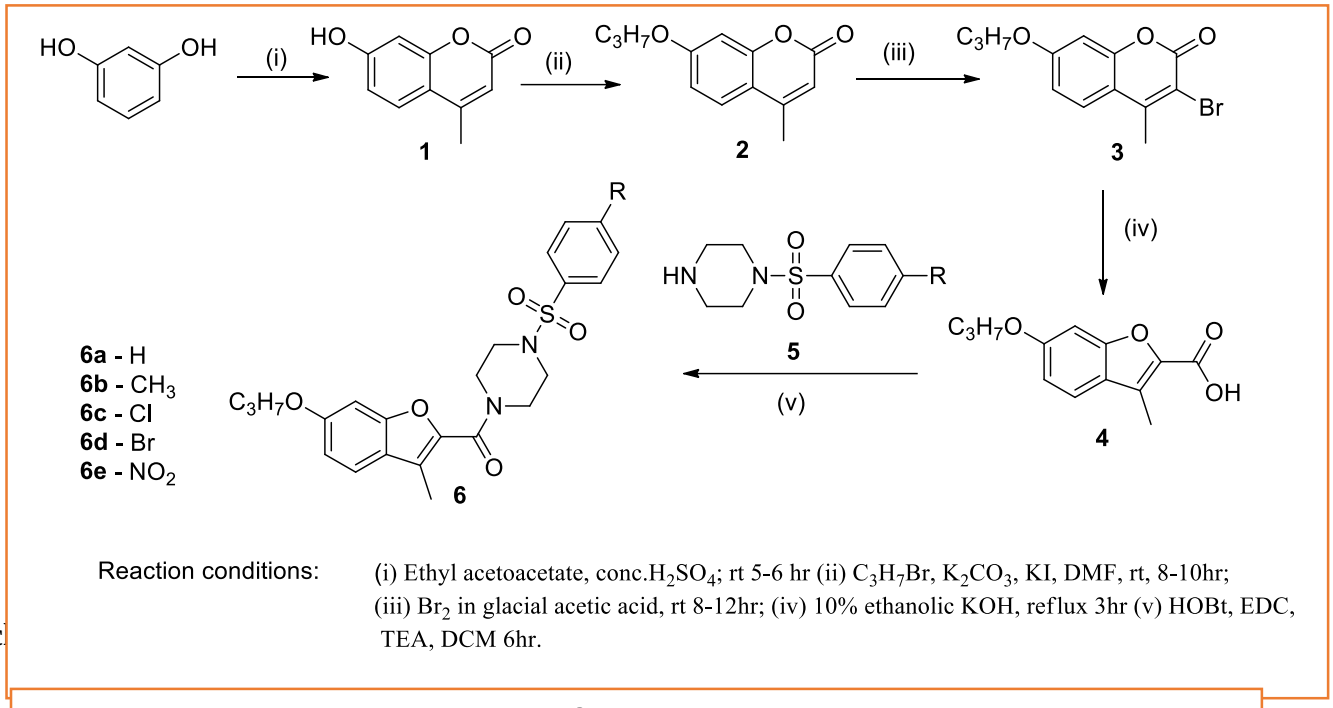
- To design and synthesize benzofuran carboxamide derivatives.
- To design and synthesize pyrazolones derivatives of 7-amino-4-methyl coumarin and 6-aminocoumarin.
- To design and synthesize 6-aminocoumarins combined them with phenyl sulphonyl piperazine and phenyl piperazines.
- Anticancer activity of all synthesized compounds by using MTT assay.to screen the most active compound and study Ethidium Bromide/Acridine Orange staining assay, LDH assay.
- To explore coumarin as a liquid crystal design and synthesis of coumarin based unsymmetric chalcone derivatives and schiff base derivatives of coumarin
- To characterize all the compounds with spectral techniques.
- To study all compounds for its mesomorpic properties and DFT study.

Chapter 2: Design, synthesis and anticancer activity of amide derivatives of substituted 3-methyl benzofuran-2-carboxylic acid

Research Methodology

We have designed and synthesized amide derivatives of substituted 3-methyl-benzofuran-2-carboxylic acid with aryl sulfonamide piperazines, aryl hydrazides and aryl hydrazines. All the synthesized compounds were screened for their anticancer activity against lungs cancer cell line(A549) and breast cancer cell line (MCF7) using MTT assay. Compound **8b** showed excellent activity against lungs cancer cell line (A549) with IC_{50} value of 0.858 µM and compound **6d** showed good activity against breast cancer cell line (MCF7) with IC_{50} value of 2.07 µM. Hence, compounds 10d and 12b were studied further for their mechanism of cytotoxicity by using EtBr/AO and LDH assay in respective cell lines. The cytostatic potential of compound **6d** and **8b** was uncurtail by Trypan blue exclusion assay and active involvement of ROS was quantified using DCFH-DA dye. The drug-likeliness and toxicity predictions were done using in-silico-based SwissADME and ProTox-II webserver, which confirmed negligible toxicity (Class IV)

Scheme-1



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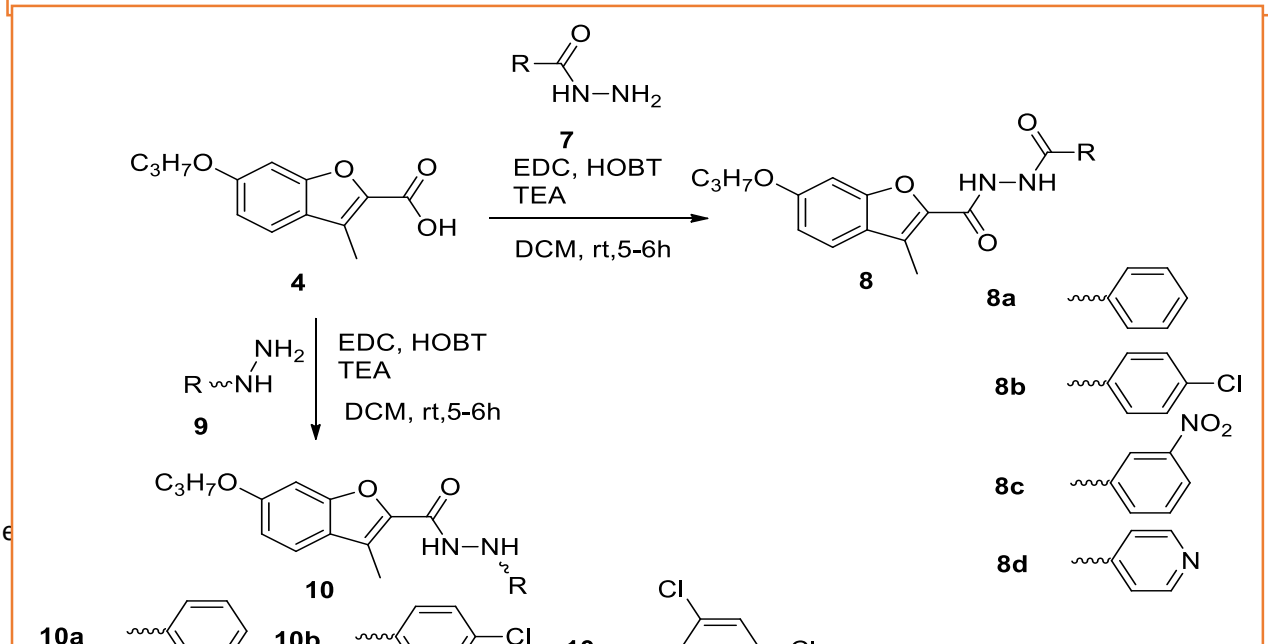


The

All synthesized compounds are characterized by ^{1}HNMR, ^{13}CNMR, IR and Mass. Compounds screen for their anticancer activity against- **1) A549-Lung cancer cell line 2) MCF-7 Breast cancer cell line**

Key Findings:

Table 1: Anticancer activity against A549 (Lungs cancer cell line), MCF-7 (Breast cancer cell line) for compounds **6a-e, 8a-d** and **10a-c**.

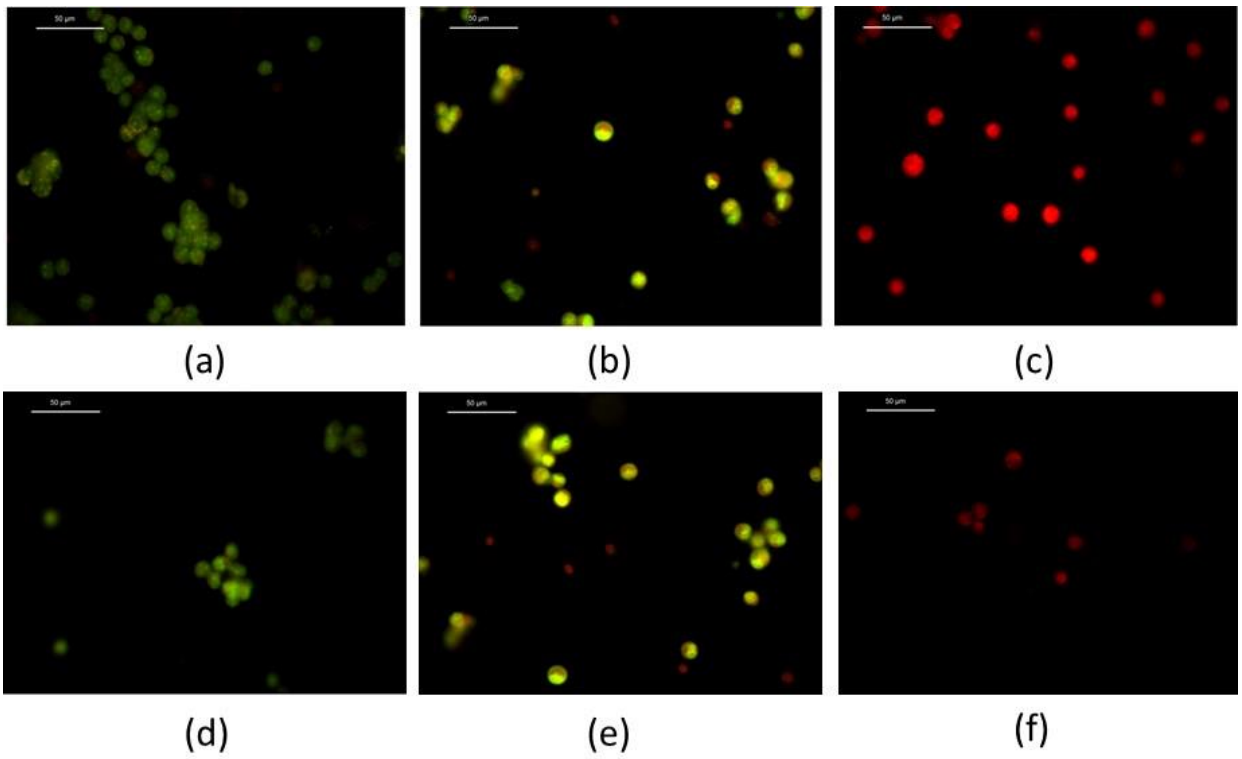
Compound	IC_{50} µM[a]	
	A549	MCF7
6a	16.77±.034	10.22±.045
6b	3.08±.003	4.9±.0239
6c	8.97±.092	2.74±.026
6d	1.504±.056	**2.07±0.65**
6e	1.04±.006	4.391±.032
8a	16.41±.401	13.45±.25
8b	**0.858±.0049**	7.756±1.03
8c	9.07±0.21	7.49±.042
8d	22.61±.96	4.86±0.72
10a	3.66±.073	9.34±.019
10b	1.822±.029	4.19±1.27
10c	1.86±.023	23.1±1.02
Fluorouracil	11.13 ±0.083	45.04 ±1.02

[a]IC_{50} values were determined based on MTT assay using GraphPad Prism software

Conclusion:

The cytotoxic studies of compound **8b** and **6d** have shown the apoptosis in both A549 and MCF-7 cell lines using LDH assay, Trypan blue assay and the EtBr/AO assay. The increased level of ROS concentration in compound **8b** and **6d** in A549 and MCF-7 cell line at IC_{50} value confirmed

apoptosis. The In-silico based ADME and toxicity study of **8b** and **6d** compounds indicated that both compounds showed drug-likeliness and can be studied further in detail as anticancer drug.

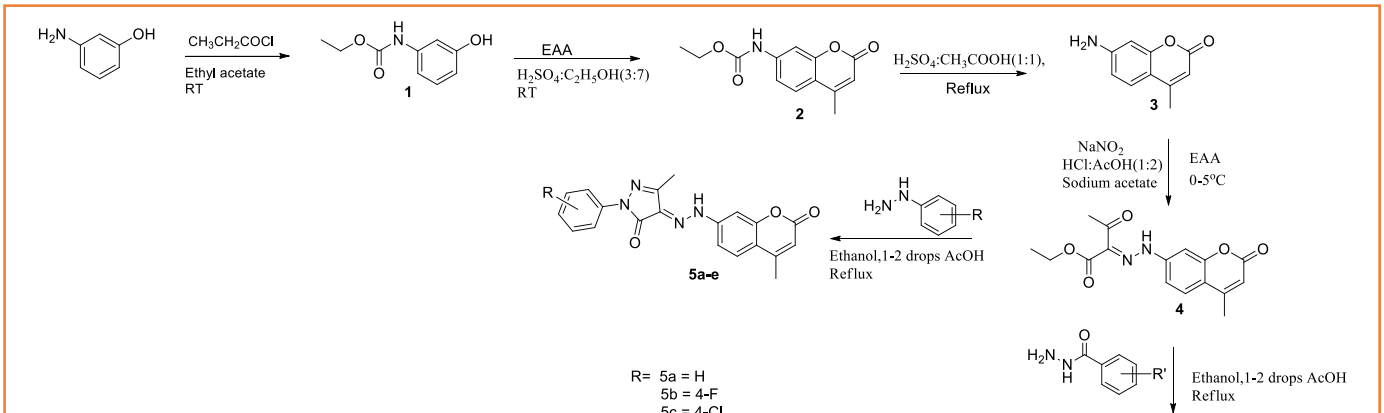


Chapter-3a: Design and synthesis of pyrazolone derivatives of coumarin as anticancer agents

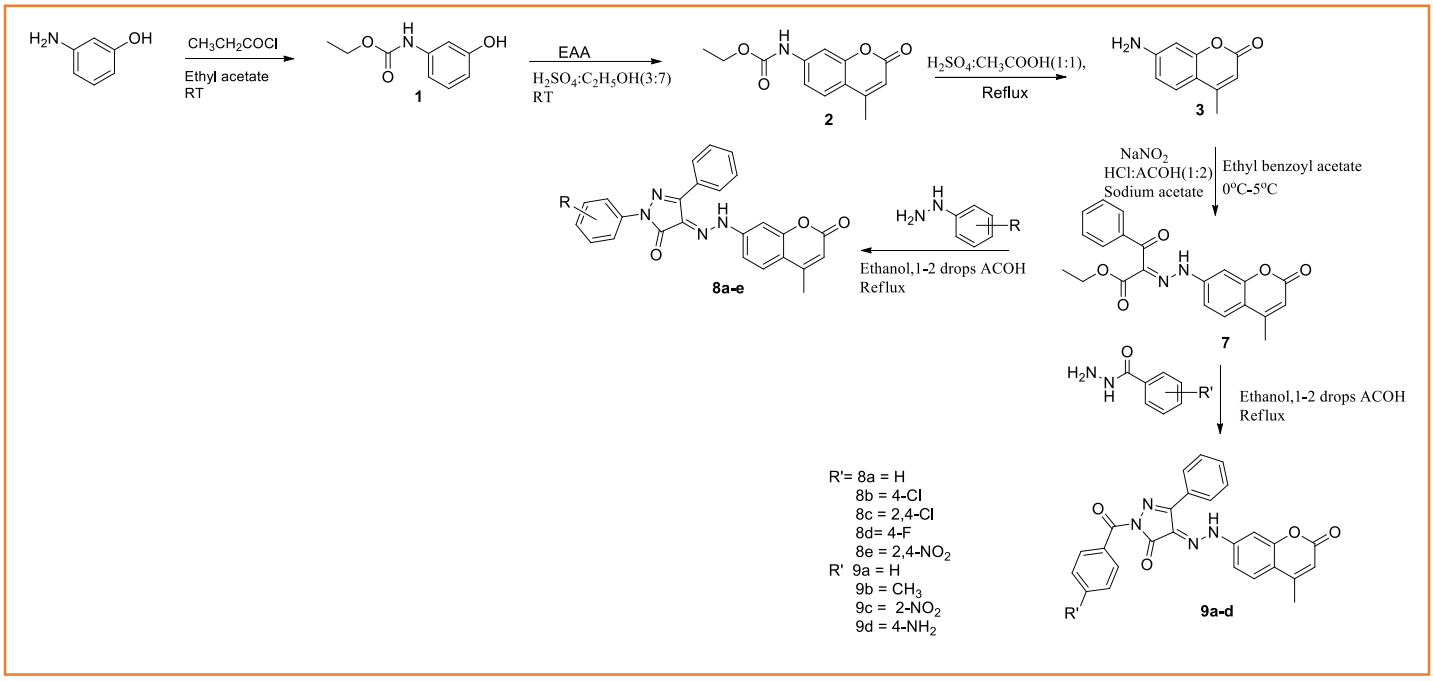
Research Methodology:

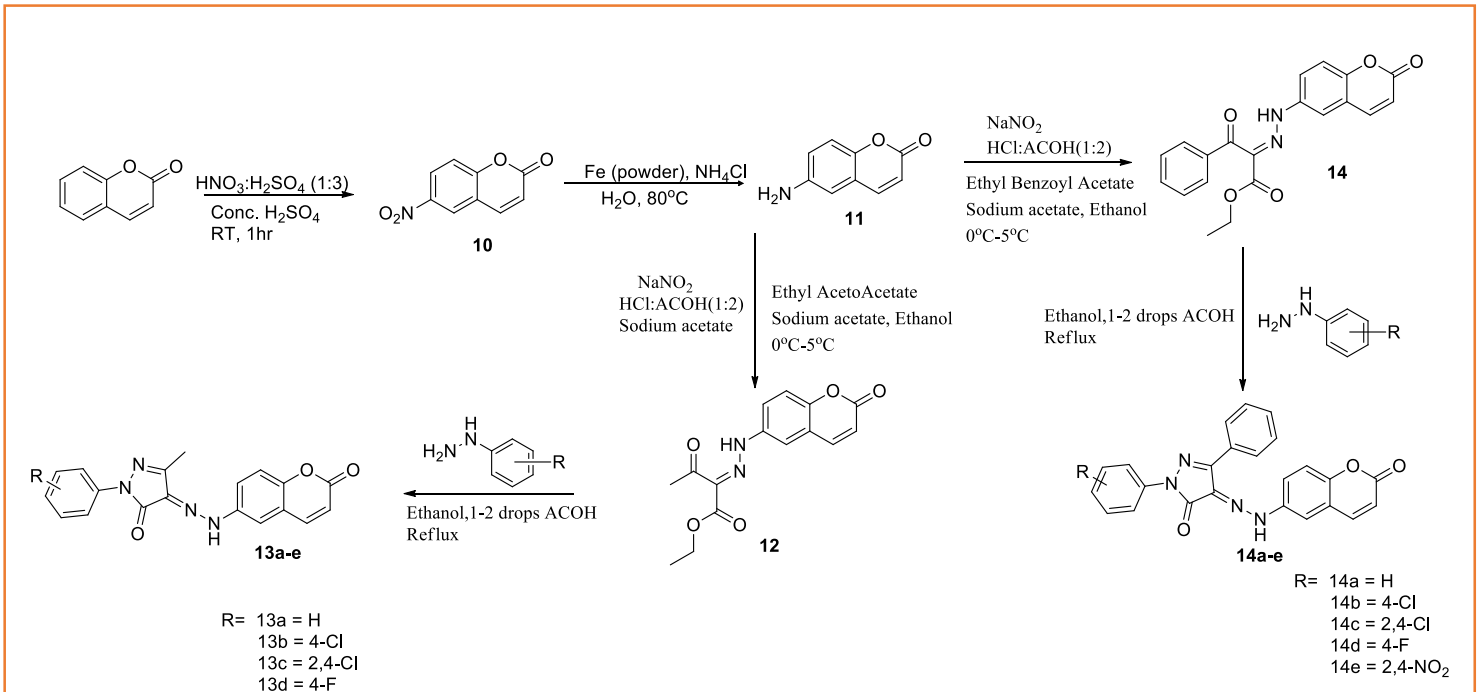
In this chapter Pyrazolone derivatives of 7-amino,4-methyl coumarin and 6-amino coumarin was synthesized for their anticancer activity. Characterizations of all synthesized compounds were carried out by ^{1}HNMR, ^{13}CNMR, Mass and IR.

Scheme-1



Scheme-2


CH3CH2COCl
Ethyl acetate
RT
1
EAA
H2SO4:C2H5OH(3:7)
RT
2
H2SO4:CH3COOH(1:1),
Reflux
3
NaNO2
HCl:ACOH(1:2)
Sodium acetate
Ethyl benzoyl acetate
0°C-5°C
7
Ethanol,1-2 drops ACOH
Reflux
8a-e
Ethanol,1-2 drops ACOH
Reflux
9a-d
R'= 8a = H
8b = 4-Cl
8c = 2,4-Cl
8d= 4-F
8e = 2,4-NO2
R' 9a = H
9b = CH3
9c = 2-NO2
9d = 4-NH2


HNO3:H2SO4 (1:3)
Conc. H2SO4
RT, 1hr
10
Fe (powder), NH4Cl
H2O, 80°C
11
NaNO2
HCl:ACOH(1:2)
Ethyl Benzoyl Acetate
Sodium acetate, Ethanol
0°C-5°C
14
NaNO2
HCl:ACOH(1:2)
Sodium acetate
Ethyl AcetoAcetate
Sodium acetate, Ethanol
0°C-5°C
12
Ethanol,1-2 drops ACOH
Reflux
13a-e
Ethanol,1-2 drops ACOH
Reflux
14a-e
R= 13a = H
13b = 4-Cl
13c = 2,4-Cl
13d = 4-F
R= 14a = H
14b = 4-Cl
14c = 2,4-Cl
14d = 4-F
14e = 2,4-NO2

All synthesized compounds screen for their anticancer activity which are shown in table-1 with their IC_{50} value in micromolar concentration. It was observed that pyrazolone with phenyl group show improvement in the anticancer activity of the drug.

Key Findings:

Table 3a.1: Anticancer activity against A549 (Lungs cancer cell line), MCF-7 (Breast cancer cell line) for compounds **10a-c, 11a-d, 12 and 13**

Compound	IC_{50} µM[a]	
	A549	MCF-7
10a	141.7±2.4	86.9±6.08
10b	2.32±0.06	18.6±0.08
10c	1145±17.9	624.0±12.2
11a	62.40±3.6	32.6±4.02
11b	1.26±0.005	5.9±0.074
11c	809.3±7.69	301.2±8.5
11d	167.8±3.98	206.5±10.23
12	382.0±12.1	417.5±13.2
13	2.34±0.063	10.3±0.056
Fluorouracil	11.13 ±0.083	45.04 ±1.02

[a]IC_{50} values were determined based on MTT assay using GraphPad Prism software

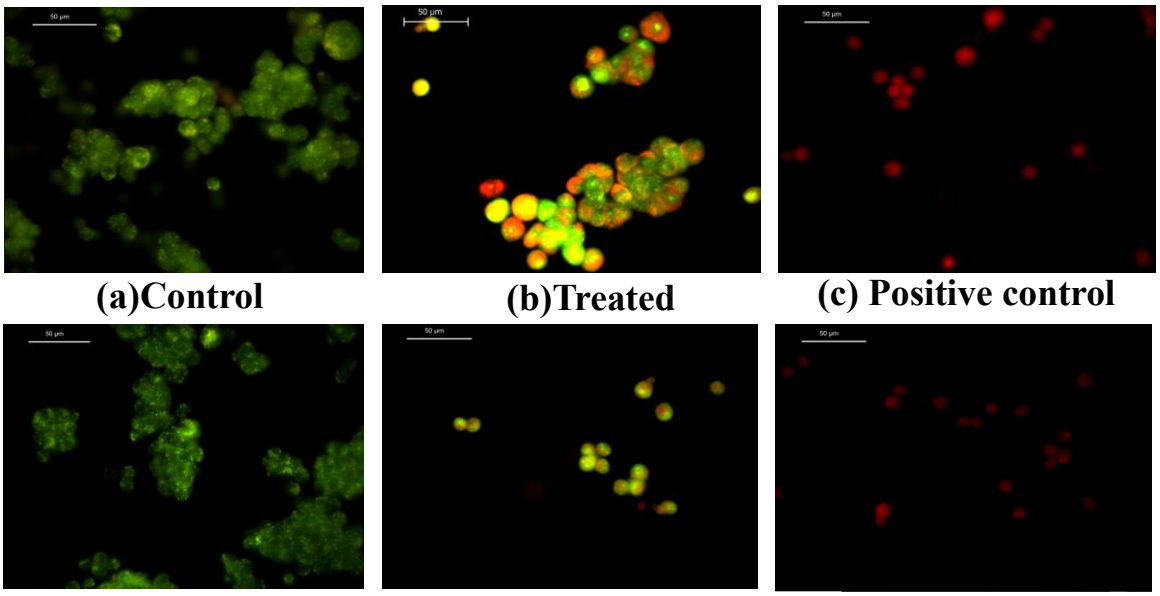
Table 3a.2: Anticancer activity against A549 (Lung cancer cell line), MCF-7 (Breast cancer cell line) for compounds **17a-d** and **19a-d**

Compound	IC_{50} µM[a]	
	A549	MCF-7
17a	1.44±0.068	9.14±0.98
17b	12.48±1.06	8.60±0.056
17c	**1.22±0.048**	65.29±1.81

17d	34.34±1.67	59.60±3.8
19a	4.11±0.048	2.21±0.014
19b	3.32±0.058	**1.66±0.015**
19c	6.10±0.050	14.00±0.011
19d	2.20±0.053	19.76±0.089
Fluorouracil	11.13 ±0.083	45.04 ±1.02

[a]IC_{50} values were determined based on MTT assay using GraphPad Prism software

Ethidium bromide and Acridine orange assay- Etbr/AO assay was carried out for most potent anticancer compounds shows apoptosis pathway



(a)Control (b)Treated (c) Positive control

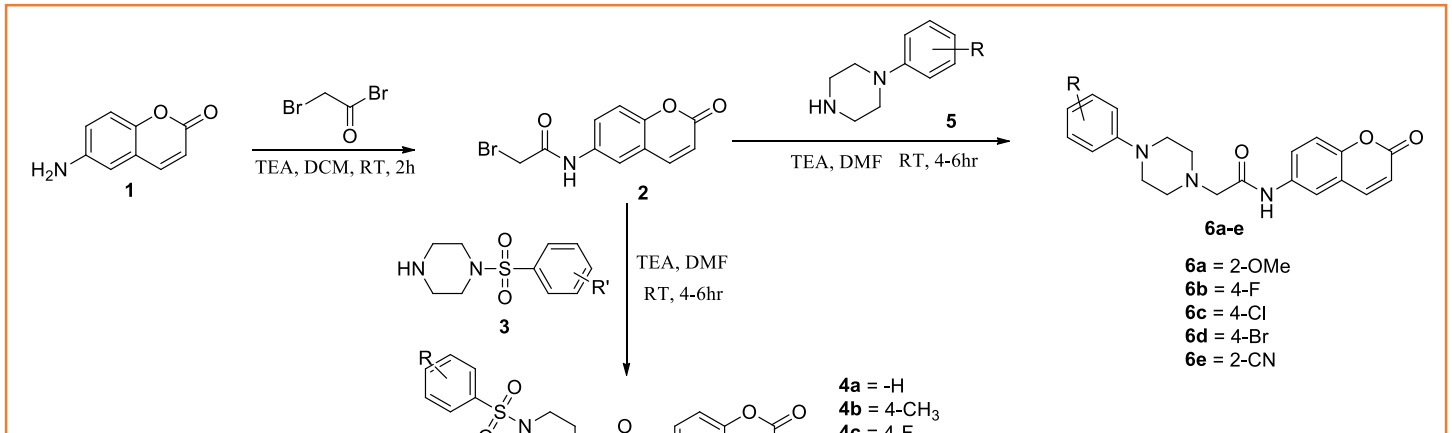
(d)Control (e)Treated (f)Positive control

Chapter-3b- Design and synthesis of piperazine derivatives of coumarin as anticancer agent

Research Methodology:

In this chapter design and synthesized amide derivatives of 6-aminocoumarin combined them with phenyl sulphonyl piperazines and phenyl piperazines to evaluate the anticancer activity of all synthesized compounds by using MTT assay.

Scheme:



Anticancer activity by using MTT assay against A549 (lung cancer cell line) and MCF-7 (breast cancer cell line)

Key Findings:

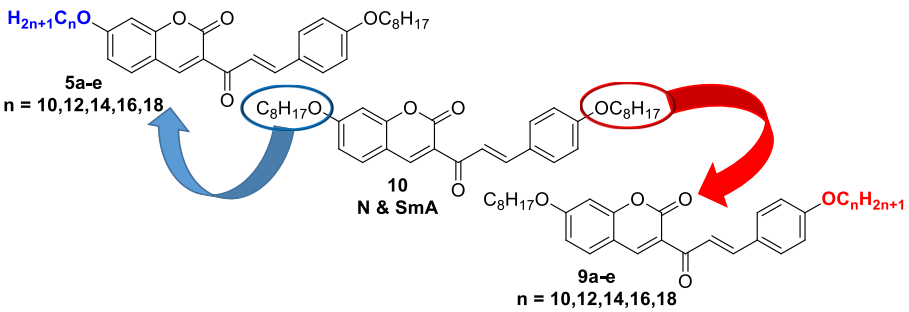
Comp	R =	A549 IC_{50}^{a} (μM[a])	MCF7 IC_{50}^{a} (μM[a])
4a	H	3.39±.15	8.14±.033
4b	4-CH3	460±5.66	50.413±1.71
4c	4 -F	5.62±.053	338.1±2.52
4d	4-Cl	**2.06±.057**	4.93±.029
4e	4 -Br	92.62±1.23	**0.85±.03**
4f	4-NO_2	3.5±.045	3.95±.027

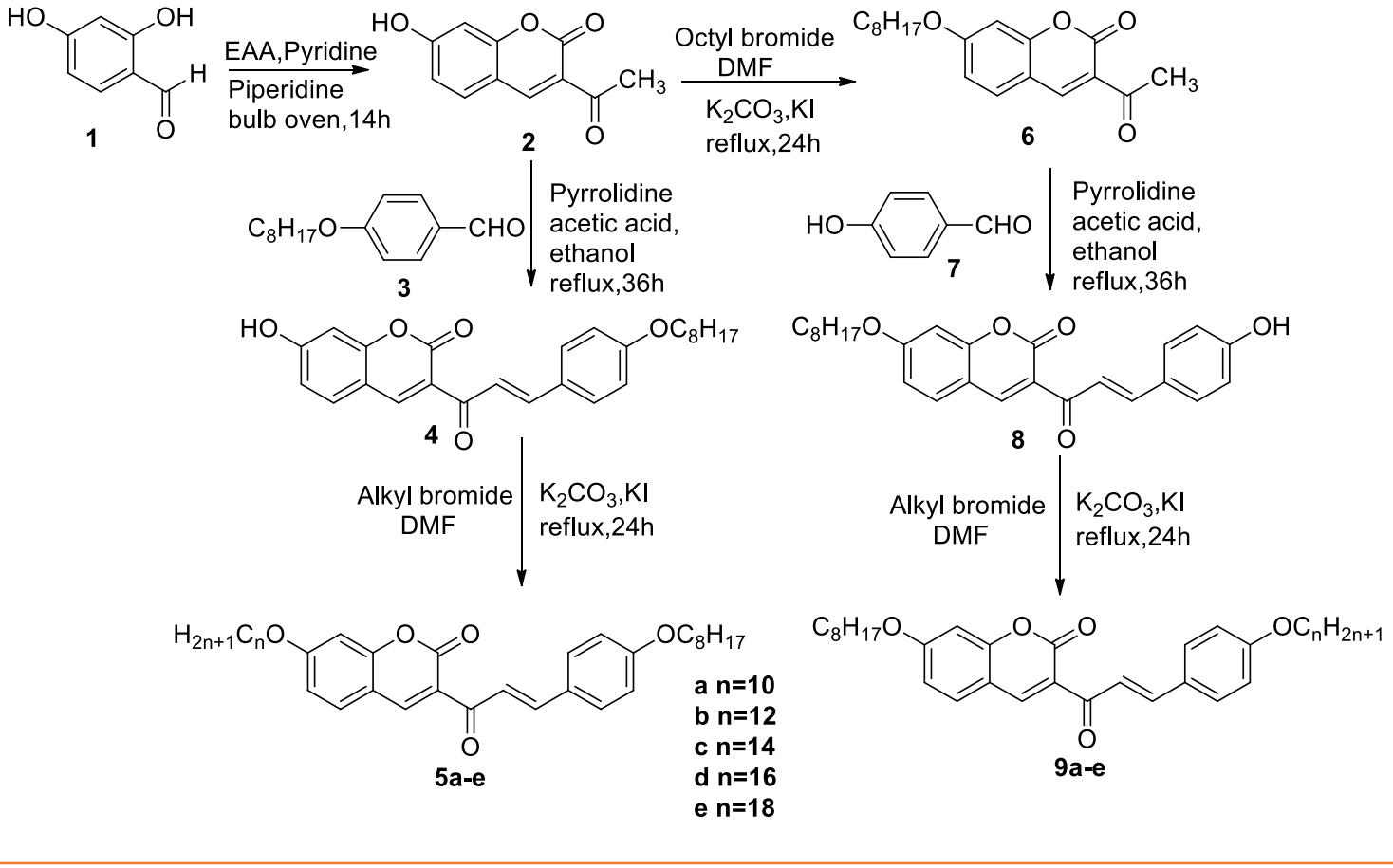
Comp	R'	A549 IC_{50}^{a} (μM[a])	MCF7 IC_{50}^{a} (μM[a])
6a	**4-F**	7.74±0.038	4.74±0.042
6b	**2-OMe**	1.7±0.059	39.17±1.6
6c	**4-Cl**	**0.4±0.032**	**0.51±0.031**
6d	**4-Br**	5.04±0.071	11.43±0.014
6e	**2-CN**	14.5±0.12	11.15±0.019

Chapter-4 Design of Unsymmetric Coumarin Chalcone Derivatives with Tunable Self-Assembling Behavior

Research Methodology:

In this chapter design and synthesize coumarin based unsymmetric chalcone derivatives. To characterize all the compounds with spectral techniques. And study all compounds for its mesomorpic properties with differential scanning calorimetry and polarizing optical microscope DFT study of all synthesised compounds.

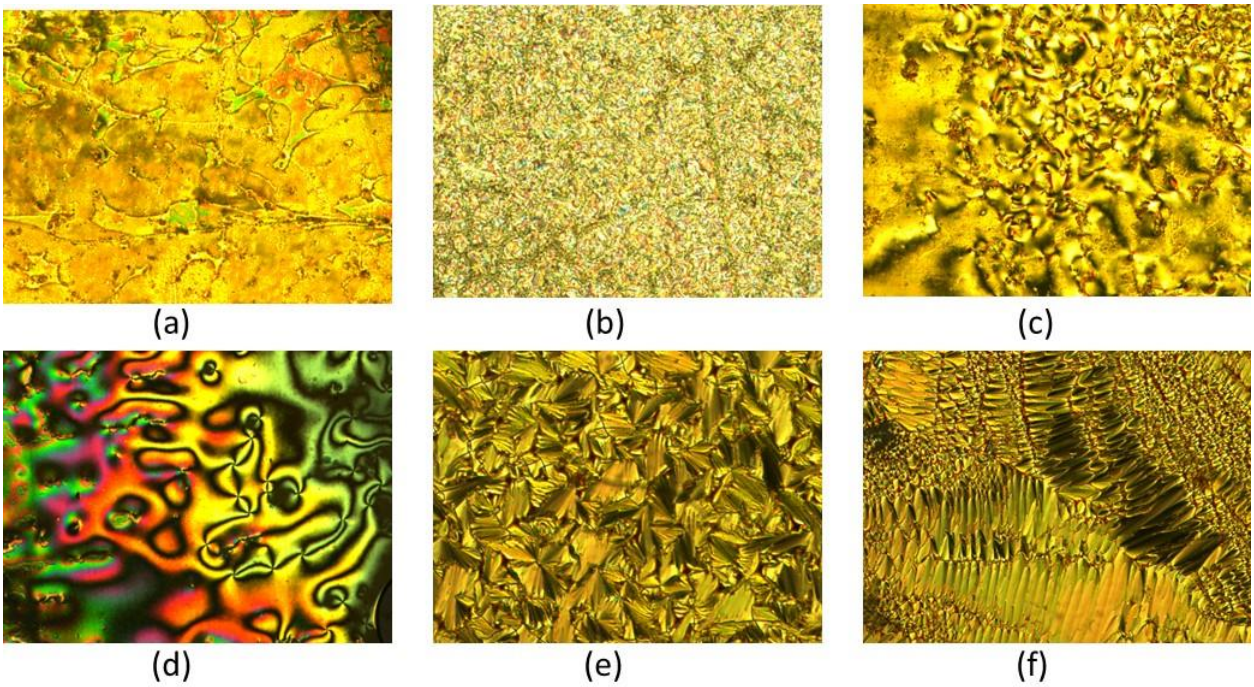




Key Findings:

Mesomorphic Study-

Further study of mesomorphic properties of all compounds by using by POM, confirmation of mesogens by using DSC and DFT calculation was carried out.



Liquid crystal phase transition (a) nematic marble for compound **5a** on cooling (b) SmC broken fan texture **5d** (c) nematic marble for compound **9a** (d) nematic schlieren texture for compound **9c** (e) SmA focal conic for compound **9d** in cooling cycle (f) SmA focal conic for compound **9d** in heating cycle

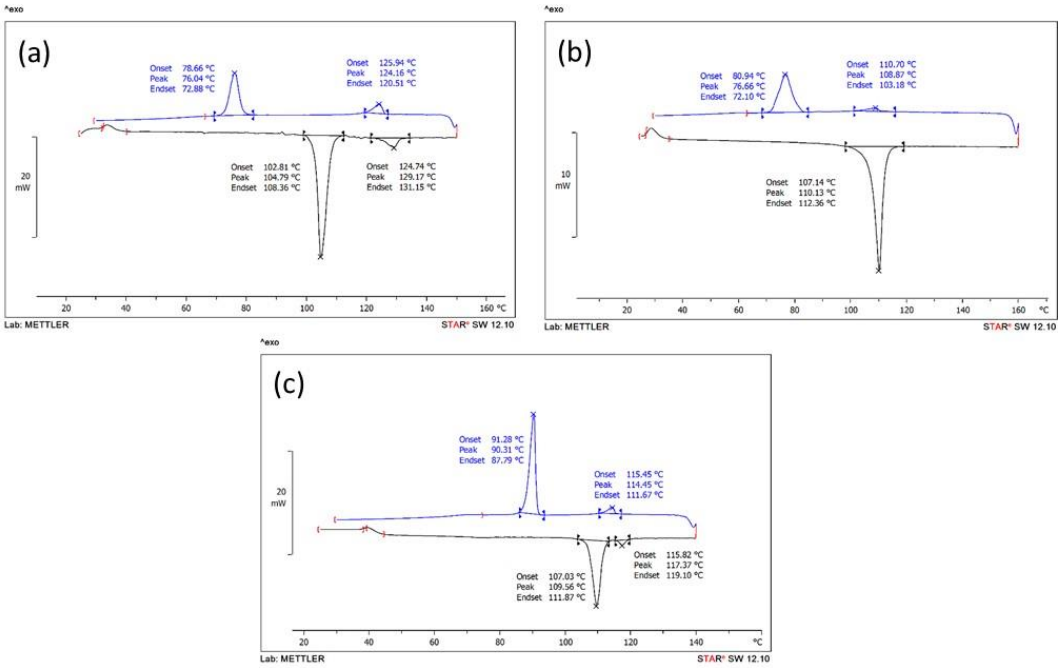


Figure 4: DSC plot in both heating and cooling cycles along with transition temperatures (a) compound **5d** (b) compound **9a** (c) compound **9d**.

DFT Study-

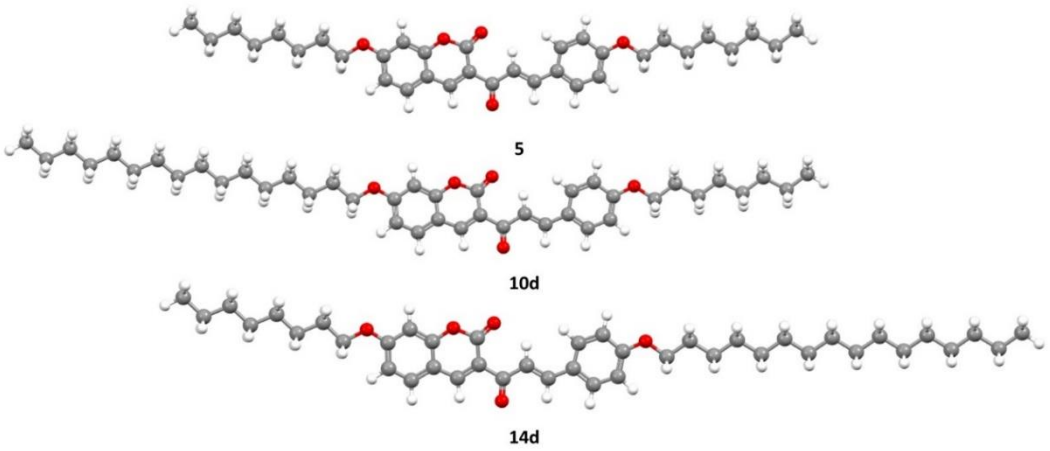


Figure 7: Calculated molecular geometry of the compounds **10**, **5d** and **9d** (Colour online).

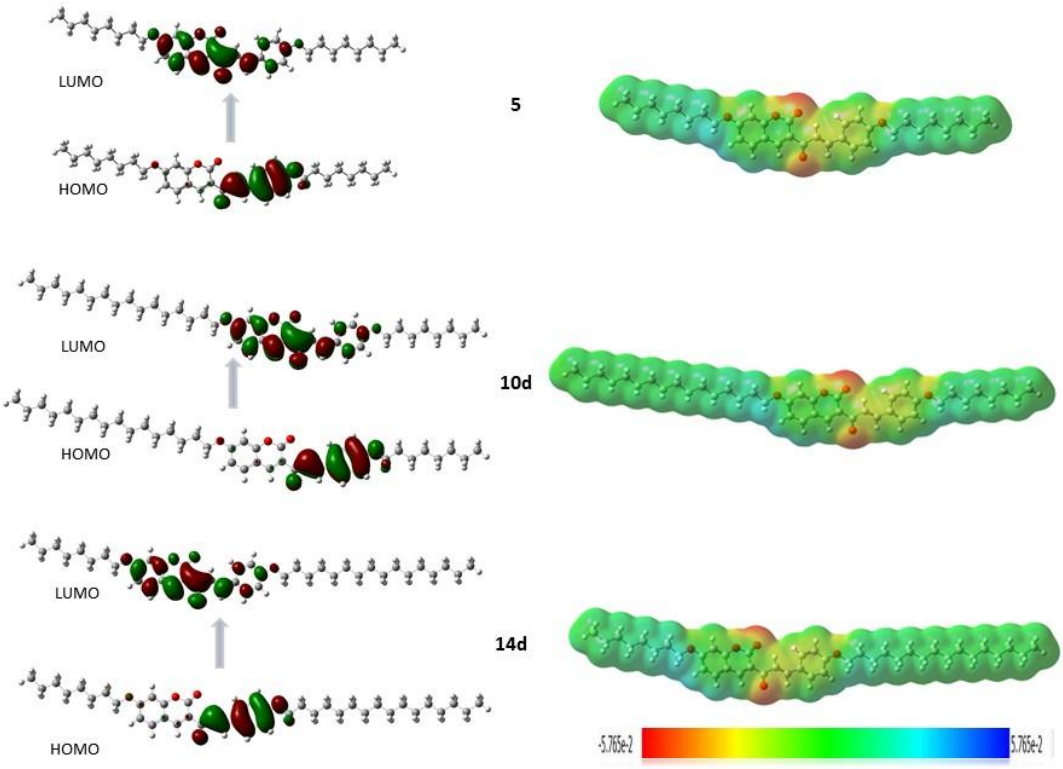
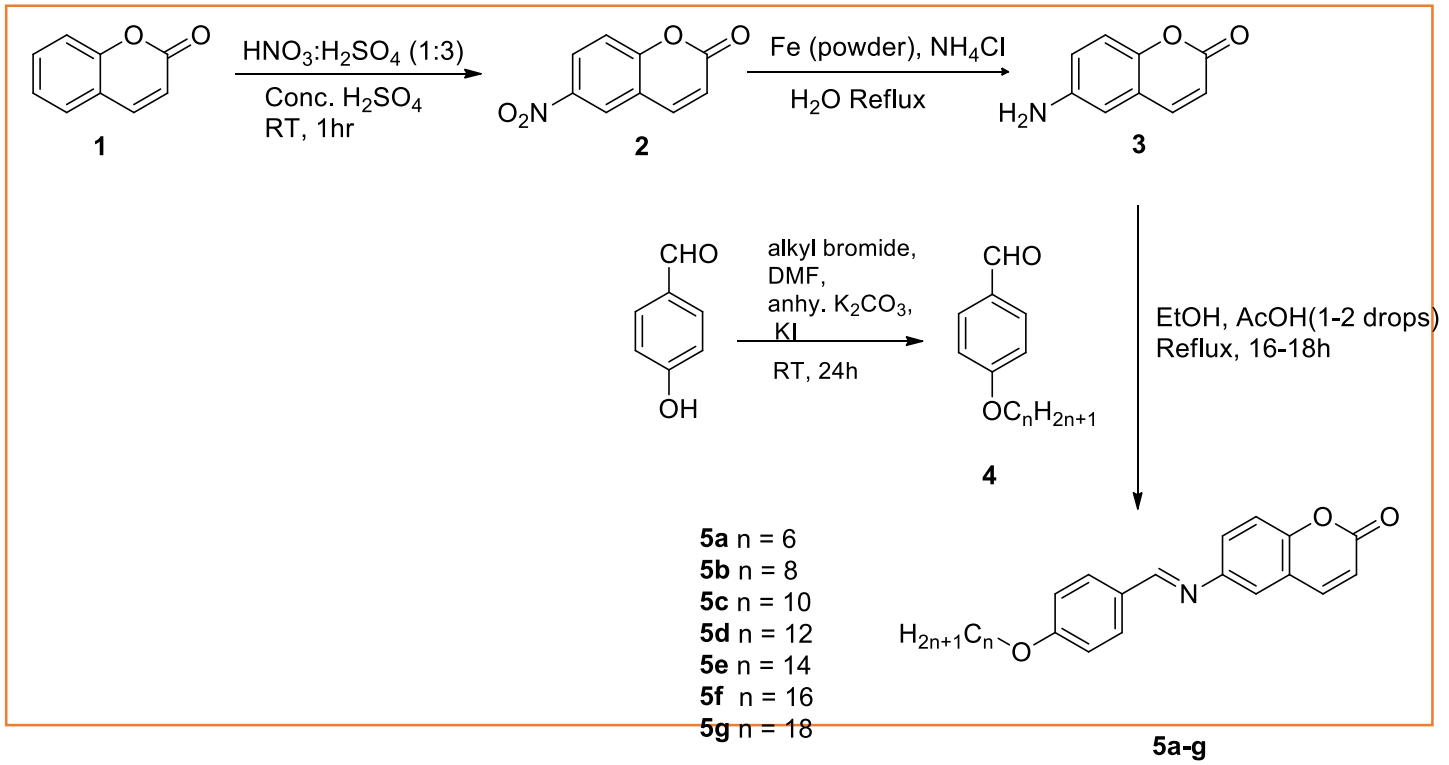


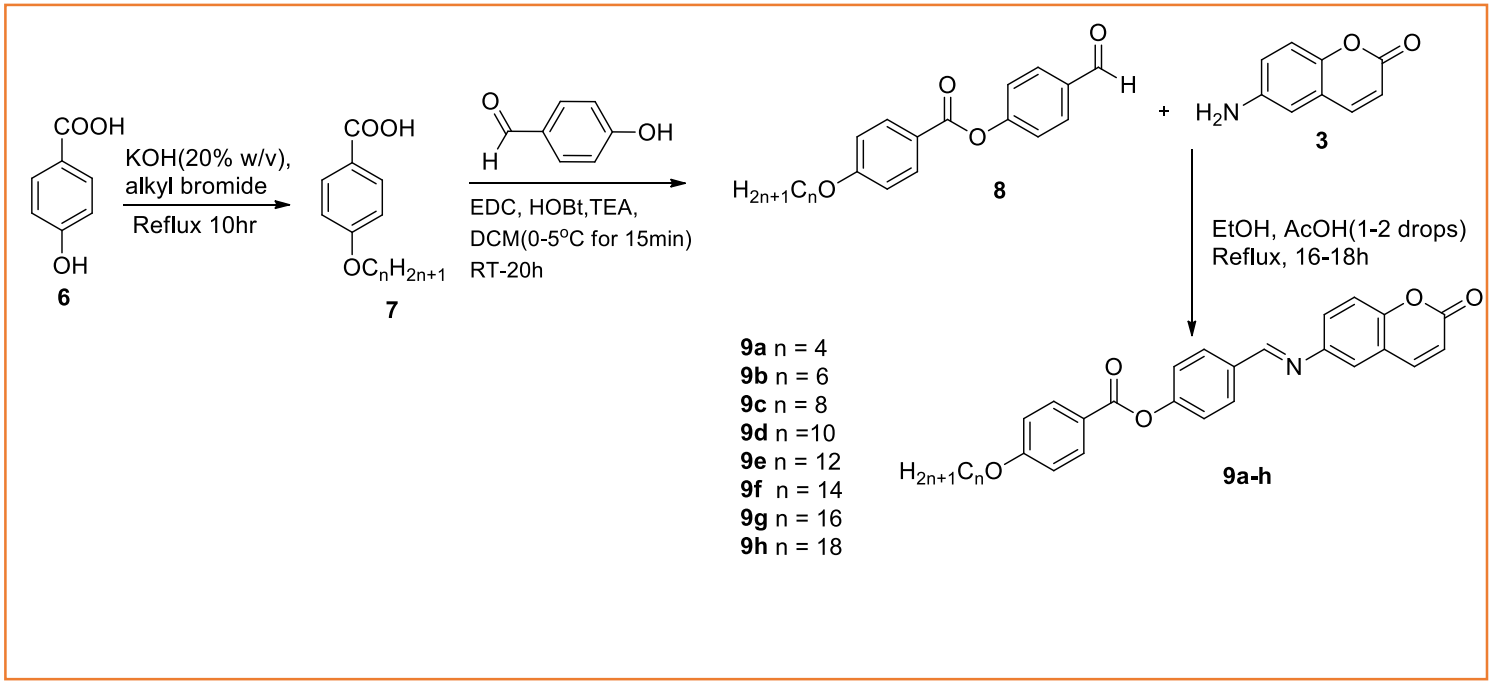
Figure 8: Frontier Molecular orbitals (FMOs) and Molecular electrostatic potentials (MEP) for the prepared compounds **5**, **10a-e** and **14a-e**.

Chapter-5: Synthesis of Schiff Base derivatives of 6-aminocoumarin as mesogens

Research Methodology:

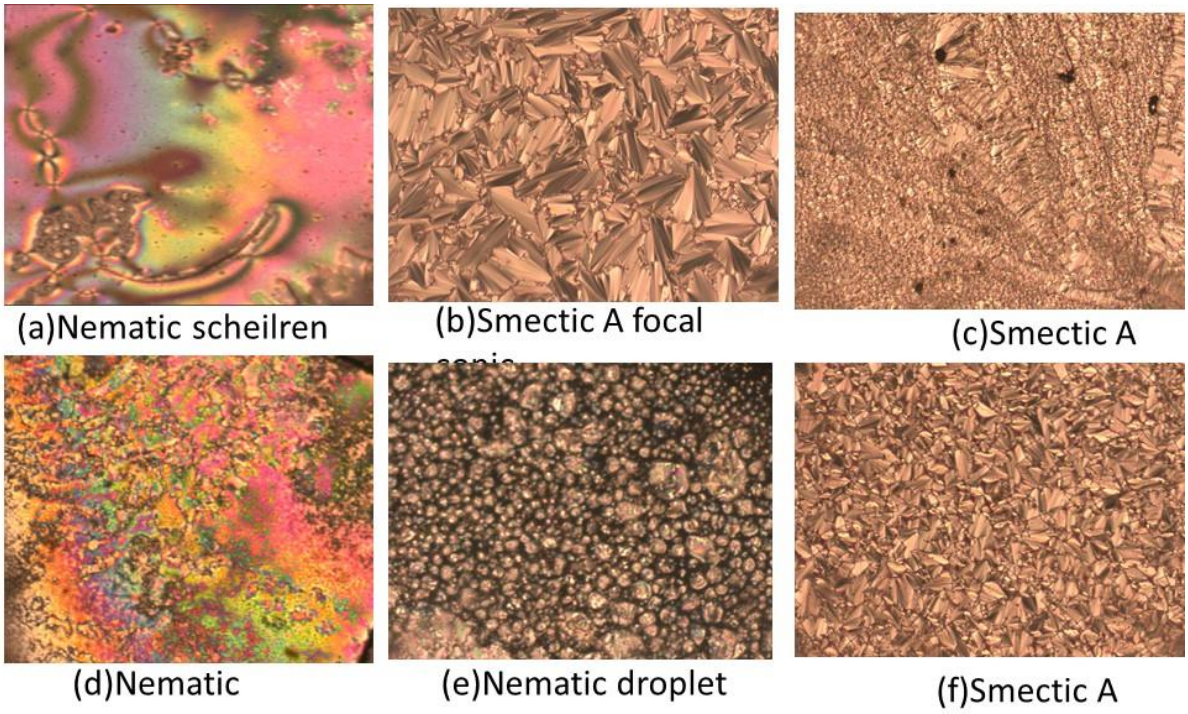
Scheme-1





Key Findings:

Mesomorphic properties-



Liquid crystal phase transition (a) nematic marble for compound **5b** on cooling (b) SmC broken fan texture **5d** (c) smectic A for compound **9c** (d) nematic schlieren texture for compound **9c** (e) nematic droplet compound **9d** in cooling cycle (f) SmA focal conic for compound **9d** in heating cycle

DSC plots-

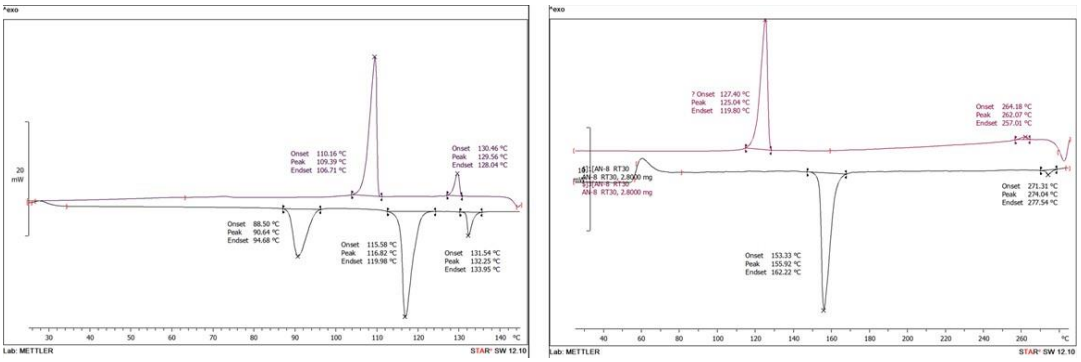


Figure 2: DSC plot in both heating and cooling cycles along with transition temperatures (a) compound **5d** (b) compound **9c**.

Powdered XRD and DFT study carried out for all synthesized compounds

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Ms. Jayashree V Patil

Research Scholar

Prof. Shubhangi S Soman

Research Supervisor

Prof. A. V. Bedekar

Head

Department of Chemistry

HEAD
Department of Chemistry
Faculty of Science
The Maharaja Sayajirao University of Baroda
Vadodara - 390002. Gujarat - INDIA

CHEMISTRY DEPARTMENT
FACULTY OF SCIENCE