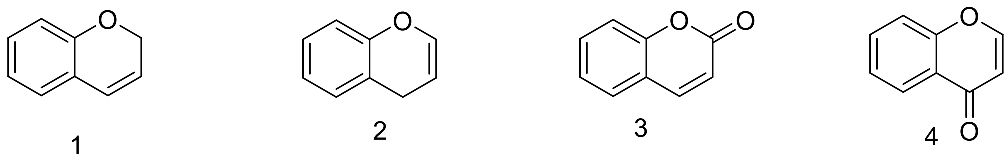
Chapter 1

Introduction to chromene derivatives and their applications

1 Introduction

1.1 Coumarin

In recent years the need of bioactive compounds containing heteroatom in branch of organic chemistry has cached the eyes of many researchers and still most intriguing in the field of medicinal chemistry. Chromene also known as benzopyran is an important class of heterocycles containing oxygen, and a chief component of many naturally occurring products. It is a bicyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring. There are two isomers of benzopyran that vary with the change of double bond with respect to oxygen, resulting in formation of 2H-Chromene and 4H-Chromene. Benzopyrones are classified as (i) benzo-α-pyrones, commonly called coumarins, and (ii) benzo-γ pyrones, called chromones, difference in both benzopyrone is mainly due to position of carbonyl carbon.



1 2H-chromene 2H-1-benzopyran | 2 4H-chromene 4H-1-benzopyran | 3 2H-chromen-2-one (Coumarin) | 4 4H-chromen-4-one (Chromone)

Figure-1.1 Structural isomers of chromene (**1**-**2**) and benzopyrone (**3**-**4**)

Chromen-2-one (Coumarin) was first isolated in 1822 from the tonka bean by Vogel [1]. The name coumarin originated from a Caribbean word 'coumarou' for the tonka tree, which was scientifically known as Coumarouna odorata Aubl or Dipteryx tetraphylla Benth [2]. Chromen-2-one was first synthesized in 1868 by the English chemist William Henry Perkin [3].

Chromen-2-one belongs to the family of benzopyrones which is a core unit of many natural products and attracted attention due to its biological and pharmacological applications, including anti-inflammatory[4-5], antioxidant[6-7], antithrombotic[8-9], antiviral[10-11], antimicrobial[12-13], antituberculosis[14], and antihyperlipidemic[15] activities. Due to the potential applications of chromen-2-one in medicinal chemistry, many efforts have been made on the design and synthesis of new chromen-2-one derivatives with improved biological activities. Chromene-2-ones exhibited antitumor activities at different stages of cancer formation through various mechanisms, for example blocking cell cycle, inducing cell apoptosis, modulating estrogen receptor (ER), or inhibiting the DNA-associated enzymes, such as topoisomerase [16]. Other than the medicinal properties, chromen-2-one has a history of importance in perfumery. It is the first synthetic substance to be used in a fragrance - Fougère Royale (Houbigant) and found in essential oils and is used in food industries for aroma [17].

(+)-Cordatolide A **5** (**Fig-1.2**) was isolated from the light petrol extract of the leaves of C. cordatooblangum. (+)-Calanolide A **7** (**Fig-1.2**) is a novel nonnucleoside reverse transcriptase inhibitor with potent activity against HIV-1 [18]. This compound was first isolated from Calophyllum lanigerum. (+)-Calanolide A accounted for anti-HIV activity, whereas (-)-calanolide A was inactive. (+)-Cordatolide A **5** (**Fig-1.2**) was isolated from the light petrol extract of the leaves of C. cordatooblangum. (+)-Calanolide A **7** (**Fig-1.2**) is a novel nonnucleoside reverse transcriptase inhibitor with potent activity against HIV-1 [18]. This compound was first isolated from Calophyllum lanigerum. (+)-Calanolide A accounted for anti-HIV activity, whereas (-)-calanolide A was inactive.

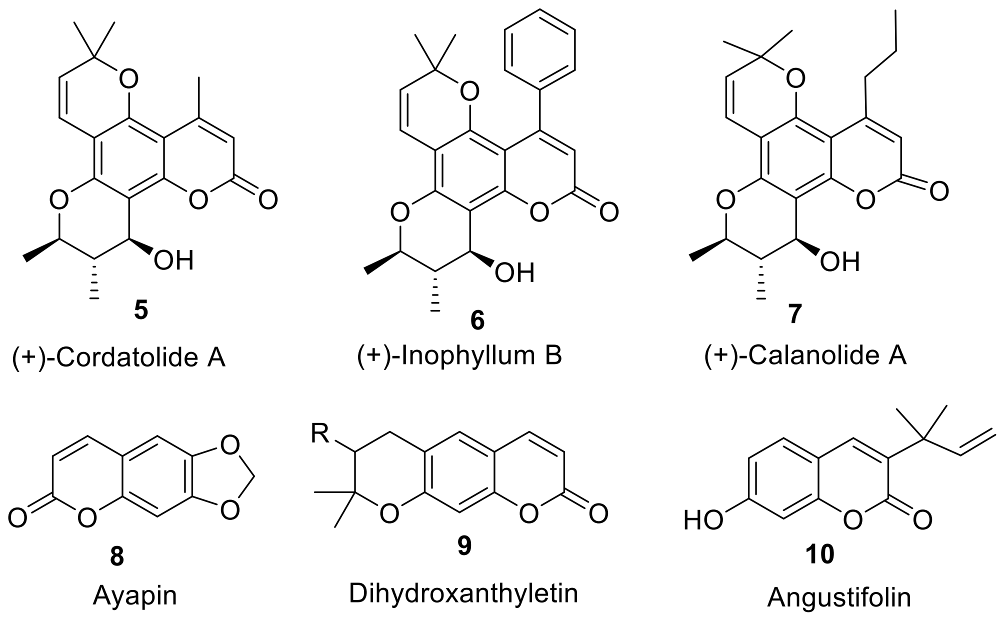


Figure-1.2 Naturally occurring chromen-2-one derivatives from plants

Ayapin **8** is also called as 6,7-methylenedioxycoumarin. Initially it was isolated from Eupatorium ayapana (Asteraceae) [19]. Later, ayapin was isolated from a number of other plants. Dihydroxanthyletin **9** isolated from seseli tortuosum and Angustifolin. Compound **10** isolated from ruta angustifolia [20]. Osthole (7-metoxy-8-isopenthenocoumarin), one of naturally-occurring coumarins isolated from dried fruits of Cnidium monnieri, Angelica pubescens and Peucedanum ostruthium is used in traditional Chinese medicine [21].

Both naturally occurring and synthetic chromen-2-one derivatives have attracted intensive attention from chemists due to their broad spectrum properties and potential for biological activities. Several natural and synthetic drugs containing coumarin scaffold are clinically well known agents. For example scopoletin (6-methoxy-7-hydroxycoumarin) is isolated from plants species and have anti-inflammatory, antioxidant and antifungal properties [22-23]. Carbochromen is used in coronary disease [24]. 7-Hydroxycoumarin (umbelliferone) **11** [25] found in a variety of plants, such as carrots, coriander, and garden angelica. It has been used as a sunscreen, a fluorescence indicator, and a dye indicator [26-27].Warfarin **14a** is a naturally occurring coumarin compound which is 4-hydroxy coumarin derivative. It is isolated from woodruff, lavender and it is used as anticoagulant agents [28-29]. Dicoumarol **15** is another naturally occurring compound containing the coumarin nucleus and is known for causing sweet clover disease in cattle [30-31]. Applications of various synthetic chromen-2-one derivatives are shown in **Fig-1.3**. On the basis of variation in coumarin ring it is possible to get different pharmacophore for many diseases.

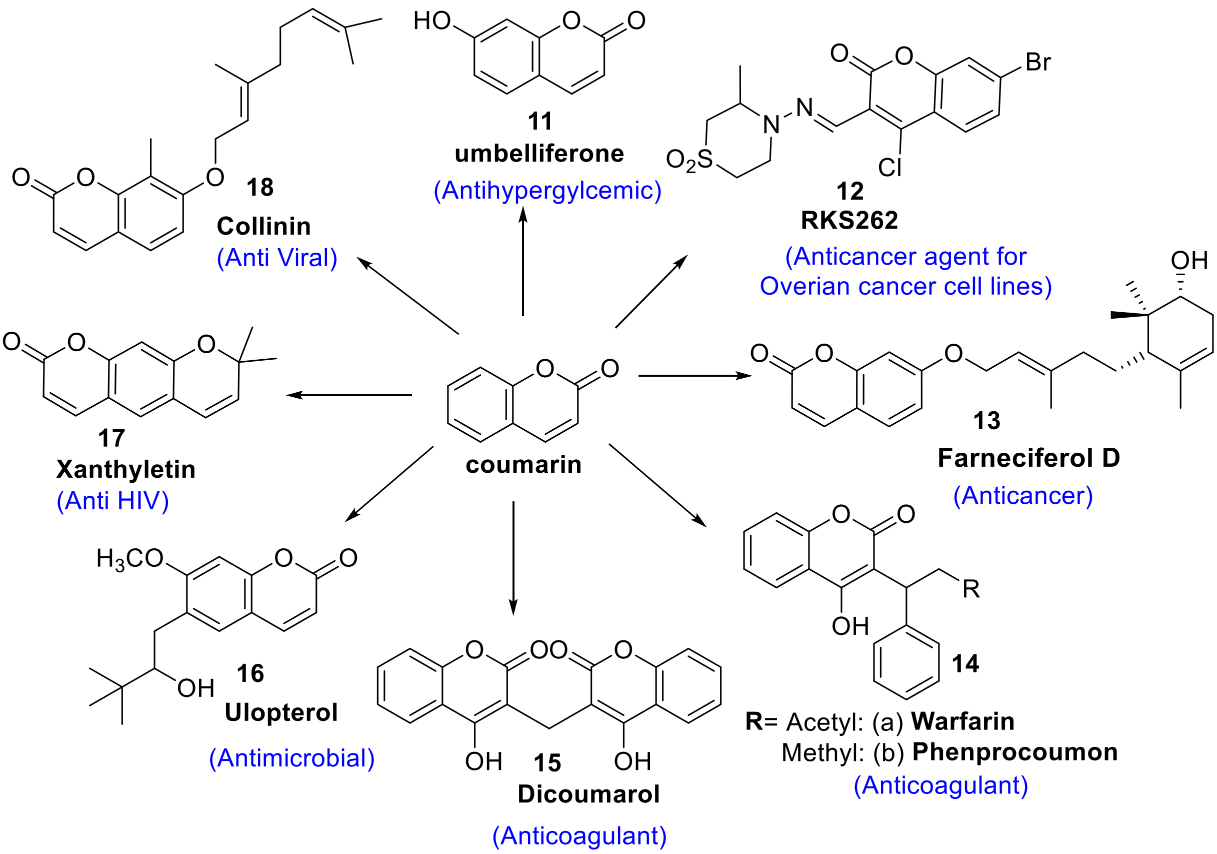
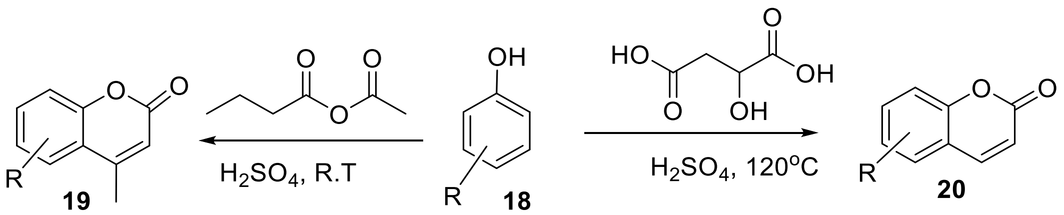


Figure-1.3 Chromen-2-one derivatives with various biological activities

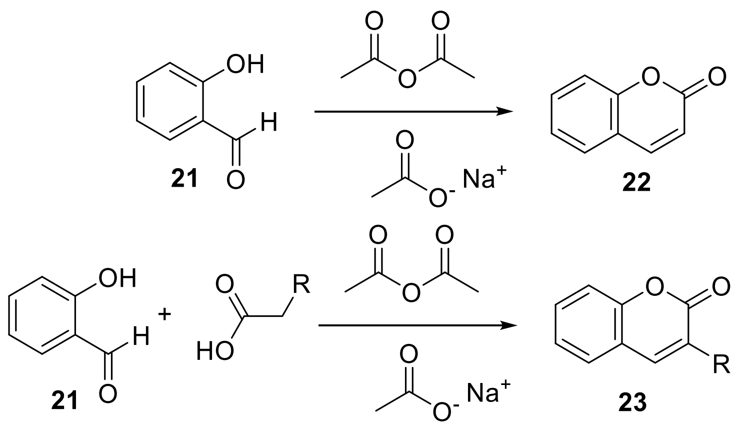
Chromen-2-one derivatives displayed excellent kinds of photochemical and photophysical properties, like in laser dye, fluorescent whiteners, fluorescent probes [32-33]. Chromen-2-one have become an interesting molecular framework to be incorporated in numerous electronic organic materials, with potential applications in OLED, solar cells and photo alignment technologies for liquid crystal displays [34-35].

1.1.1 General Synthesis of Chromen-2-one Derivatives

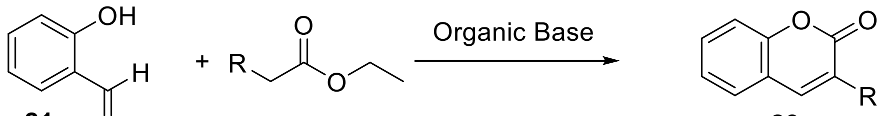
(1) Pechmann condensation: Pechmann condensation is the most widely applied method for Chromen-2-one synthesis, since it proceeds from simple starting materials i.e. phenols **18** and a β-ketoester (ethyl acetoacetate or malic acid) [36-37] and gives good yields of coumarins **19-20** with substitution in either the pyrone or benzene ring or in both. 7-hydroxy-4-methylcoumarin can be obtained in high yields upon reaction of ethyl acetoacetate with 1,3-dihydroxybenzene and condensing agent as sulphuric acid [38], Lewis acid [39], $ClSO_3H$ [40], Trifluoroacetic acid [41], Ionic liquids[42], $FeCl_3$ [43] and many others are also reported as catalyst for condensation in synthesis of coumarin derivatives.



(2) Perkin reaction: Perkin first synthesized chromen-2-one from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate. Variation on the pyrone ring can be done depending on the reagent used [44-45].



(3) Knoevenagel reaction: Synthesis of chromen-2-one derivatives from o-hydroxyaldehydes condensed with active methylene group of ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, etc., in the presence of piperidine, pyridine, and other organic bases [46].



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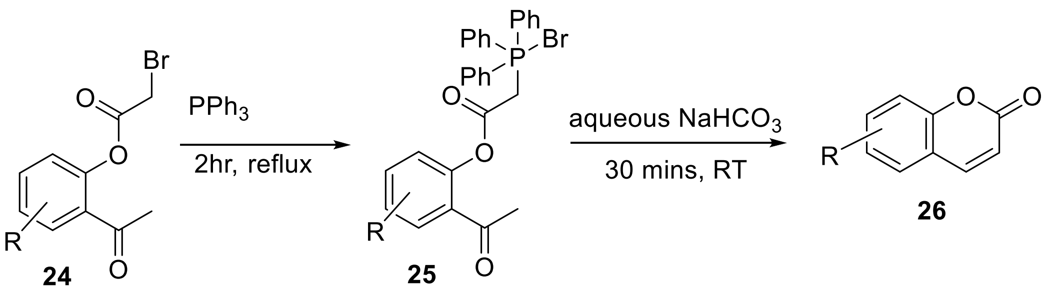
(4) Wittig reaction: Another novel method for the synthesis of chromen-2-one involves Wittig reaction between substituted o-hydroxy benzaldehydes or o-hydroxy acetophenones/benzophenones and substituted carbethoxy methylene triphenyl phosphoranes. The method has general applicability and the yields are good [47-49].



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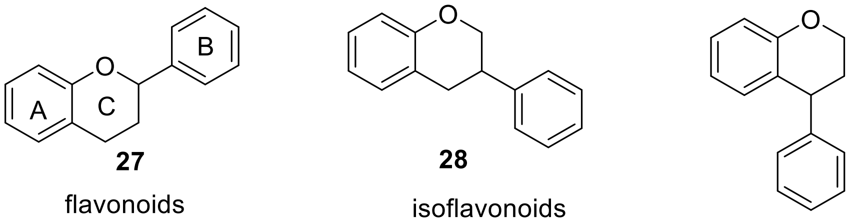
1.2 Flavone

2-phenylchromen-4-one also known as Flavones (Flavus= yellow), are a class of flavonoids based on the backbone of 2-phenylchromen-4-one (2-phenyl-1-benzopyran-4-one), flavonoids are a group of naturally occurring compounds. They are widely distributed as secondary metabolites in the plant kingdom. Flavonoids are found in fruits, vegetables, grains, barks, roots, stems, flowers, tea, and wine. They are an integral part of human diet and are most commonly known for their antioxidant activities in vitro [50]. Several other important biological activities such as hypotensive, antifungal, antibacterial, and antitumor activities [51-53] of chromen-4-one derivatives (flavones) have been reported in literature and these have increased the importance of their laboratory synthesis.



27 flavonoids

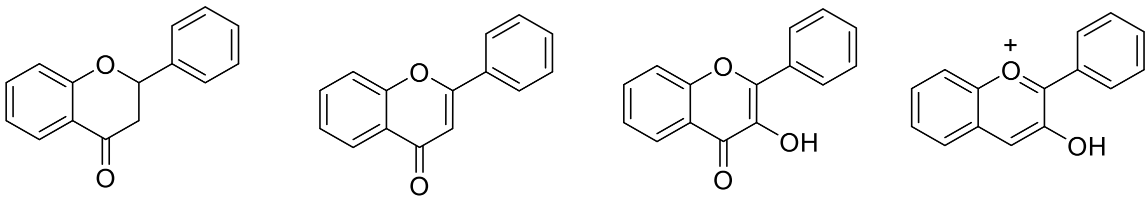
28 isoflavonoids

29 neoflavonoids

Figure-1.4 The three main classes of flavonoids differ by the position of Ring B

The flavonoids are a family of compounds with a C6-C3-C6 scaffold (**Fig-1.4**). This structural formula makes up three rings, labelled A, B and C, to give the 'flavan' scaffold 1 also known as flavonoids. There are three main classes of flavonoid compounds which depend on the positioning of Ring B; flavonoids (or 2-phenylbenzopyrans) **27**, isoflavonoids **28**, and neoflavonoids **29** (**Fig-1.4**). Flavonoids incorporate their Ring B at the 2nd position of Ring C, isoflavonoids indicated phenyl ring B at the 3rd position, and neoflavonoids at the 4th position. The flavonoids and related compounds which also contain the C6-C3-C6 backbone, include the chalcones (which do not have a Ring C but are used synthetically to access numerous flavonoid structures) and the aurones.

Flavonoids in which the B ring is linked at the 2nd position can be further subdivided into several subgroups on the basis of the structural features of the C ring. These subgroups are (**Fig-1.5**) flavanones **30**, flavones **31**, flavanols or catechins **32**, anthocyanins **33** [54-56].



30 flavanone **31** flavone **32** flavonol **33** anthocyanin

Figure-1.5 Subclasses of flavonoids

Different oxidation states and different substituents contribute to the diversity of flavonoid structures. Flavonoids play an important role in plant physiology and are of interest to humans as a result of biological activities. As a result of the biological activity of flavonoids, there is an interest in the development of synthetic procedures that can conveniently give access to these molecules and their derivatives [57]. All classes of flavonoids exhibit variety of biological activities, but among them, the flavones have been considerably explored. Various natural, semi synthetic and synthetic derivatives of flavones have been synthesized and evaluated for several therapeutic activities like anti-inflammatory, antioestrogenic, antimicrobial [58] anticancer [59] anti-allergic, antioxidant [60].

2-Phenylchromen-4-ones are present in fruits and vegetables which we consume inadvertently in our daily diet and they have a positive impact on our health without any major side effects. In order to explore diverse roles of 2-phenylchromen-4-ones, investigating various methods for their synthesis and structural modification of flavone ring have now become important goals of several research groups. Thus, naturally obtained 2-phenylchromen-4-one moiety having a variety of biological activities can be taken as lead compound for the synthesis of semi- and purely synthetic flavone derivatives with different functional groups at different positions of flavone skeleton. Flavones have three functional groups, including hydroxy, carbonyl, and conjugated double bond; consequently, they give typical reactions of all three functional groups. It is the diversity of this structure that gives flavones wide range of biological activity. Due to the wide range of biological activities of flavones, their structure activity relationships have generated interest among medicinal chemists. Some of the well-known naturally occurring potent bioactive flavones **34-36** are shown in **Fig-1.6** [61-63].

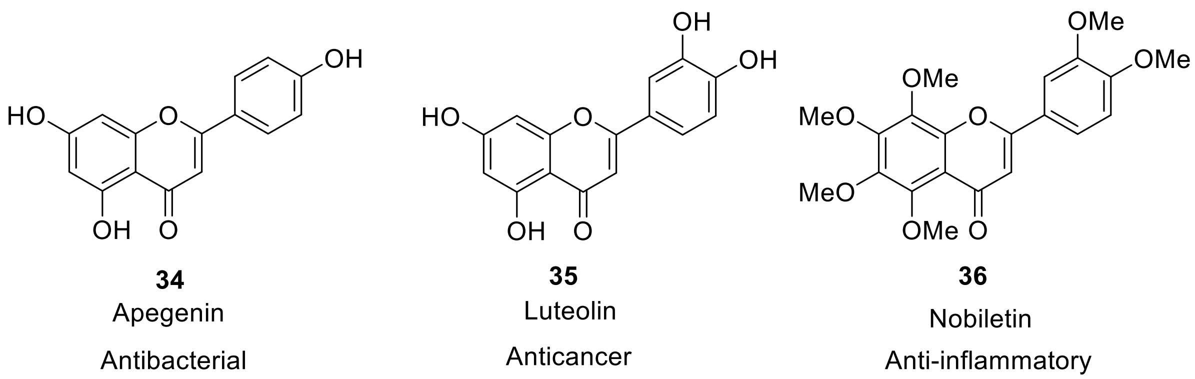
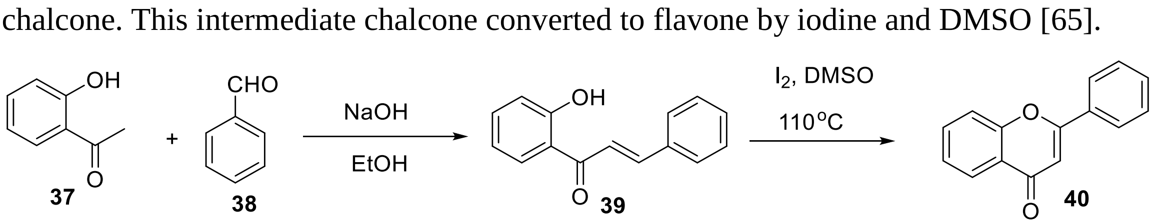


Figure-1.6 Naturally occurring bioactive flavones

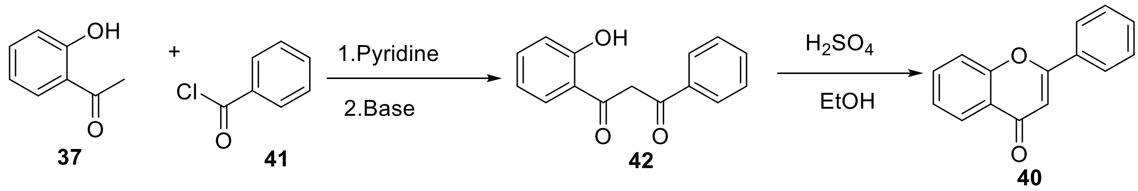
As a consequence of these vital properties shown by flavones, researchers constantly study these interesting flavonoids and come up with new strategies to synthesize them. It was reported that flavones have well known antioxidant activity; and can act by several pathways. Therefore, flavones are significantly used in pharmaceutical and food industries [64].

1.2.1 Methods to synthesize 2-phenyl chromen-4-one (flavone)

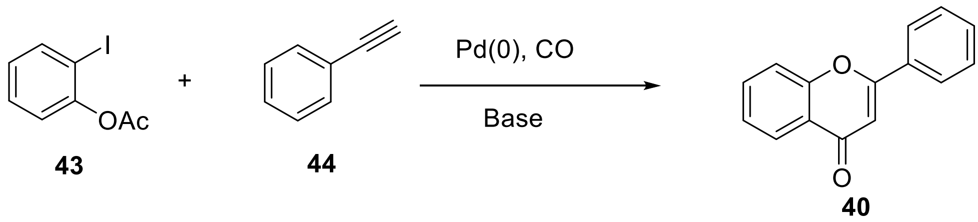
(1) Claisen-Schmidt method: 2-hydroxy acetophenone and aromatic aldehyde reacts to give chalcone. This intermediate chalcone converted to flavone by iodine and DMSO [65].



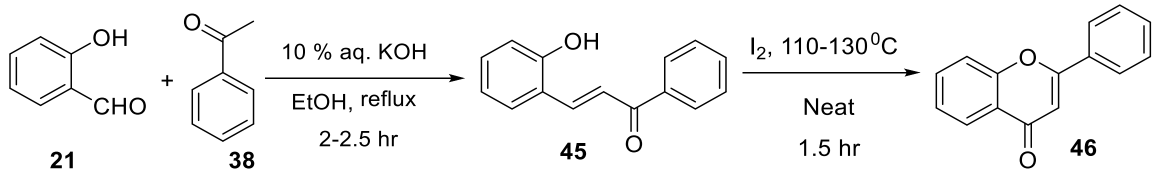
(2) Baker-Venkatraman method: Baker-Venkatraman method is most important method from which all other methods are generated. In this method 2-hydroxy acetophenone and benzoyl chloride reacts to give 1,3-dione intermediate. This 1,3-dione converted to flavone in acidic medium to give flavone[66].



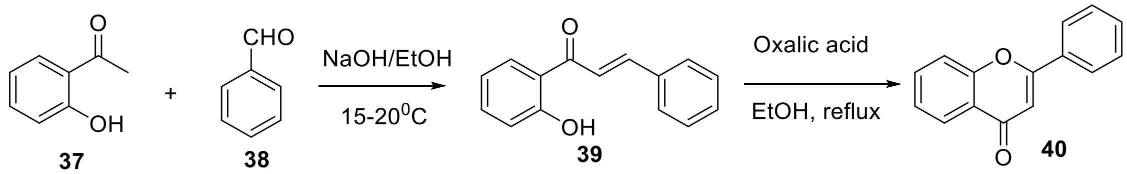
3) Hua et. al. synthesized flavone by using palladium catalyst in presence of basic conditions[67].



(4) Shashidhara et al. have reported synthesis flavone under solvent free conditions. Intermediate chalcone was prepared from ortho hydroxyl aldehyde and acetophenone. This chalcone was converted to flavone via solvent free condition [68].

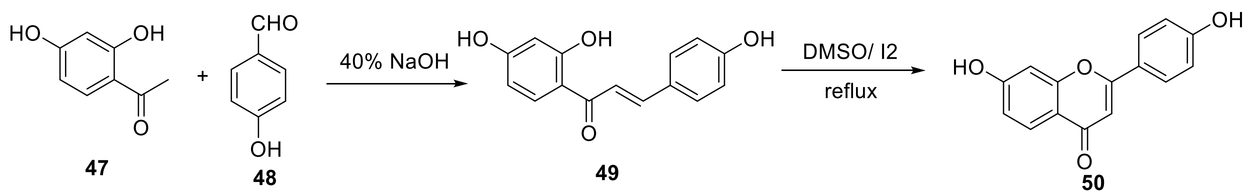


(5) Zambre et. al. have reported synthesis of flavone using oxalic acid for oxidative coupling of intermediate chalcone to flavone [69].

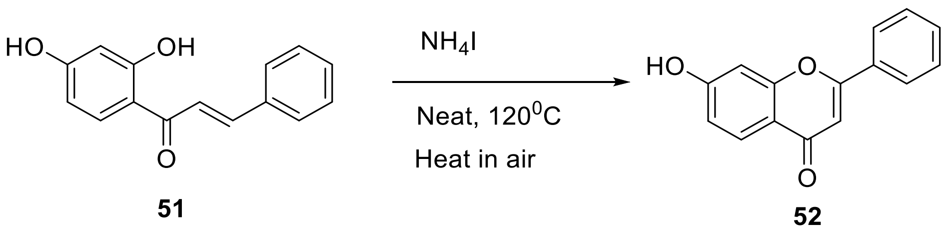


Methods to synthesize hydroxy flavones

(1) Using I_2/DMSO [70]



(2) Using ammonium iodide [71]



1.3 Cancer

Cancer is one of the prominent causes of death in the world According to WHO, around 18.1 million new cases of cancer and 9.6 million cancer deaths was estimated to occur only in 2018 [72]. In men, the highest percentage of cancer type occurs is prostate, lung, bronchus, colon, rectum, and urinary bladder. In women, cancer prevalence is highest in the breast, lung, bronchus, colon, rectum, uterine corpus and thyroid. This data indicates that prostate and breast cancer constitutes a major portion of cancer in men and women, respectively [73]. Most cancers are recognised by uncontrolled growth of cells without differentiation due to the deregulation of essential enzymes and other proteins controlling cell division and proliferation. [74-75].

Despite the tangible advances in cancer therapy, the reported incidences of the disease and the mortality have not declined in the past 30 years [76]. Understanding the molecular alterations that contribute to cancer development and progression is a key factor in cancer prevention and treatment. There are several common strategies for targeting specific cancer cells to inhibit tumor development, progression, and metastasis without causing severe side effects [77].

Chemotherapy involves use of low molecular weight drug to selectively destroy tumor cell or at least limit their proliferation, disadvantage of many cytotoxic agents include hair loss, nausea, bone marrow suppression and drug resistance. This happens due to lack of selectivity of cytotoxic agents [78]. There are more than 100 types of cancer, determining the type of cancer is important for application of treatment in most effective way. The cancer's stage will also determine the best course of treatment because early stage cancers respond to different therapies than later stages. Overall health, lifestyle, and personal preferences of an individual play a crucial role in deciding which treatment therapy will be best.

1.3.1 Chemotherapy:

Surgery, Radiation therapy and Chemotherapy are three most common ways to treat cancer. Treatment involves removing of cancerous cells or destroying them in the body with medicines or other agents. Chemotherapy is the treatment of cancer with drugs, it destroy cancer cells by hindering their growth and reproduction. In chemotherapy the drug controls cell population by cell-kill mechanism [79]. Chemotherapy consists of cytotoxic agents and anti-hormonal drugs, which reduce the proliferation of cancerous cell. Chemotherapy drugs are given intravenously by injection or oral ingestion. Chemotherapy is either used in conjunction with radiation therapy or with surgery or given alone. Chemotherapy can be used to cure cancer in many ways to keep the cancer from spreading, to kill cancer cells that can spread in other parts of the body, to slow down cancer's growth and to relieve symptoms caused by cancer. Chemotherapy is used to treat cancer cells that have metastasized to other parts of the body, because they travel throughout the body in the bloodstream. Use of chemotherapy is more promising to cure and control cancer.

Chemotherapeutic drugs are divided into several categories depending on how they interact with specific sites within the cancer cells and which specific phases of the cell cycle are blocked. Cytotoxic agents are divided in a wide range according to its mechanism e.g., alkylating agents, DNA intercalators, topoisomerase inhibitors, tubulin binders and many others.

Types of drugs that interact with DNA: Chemotherapy drugs can be divided into many groups on basis of how they work and their chemical structure. Because some drugs act in more than one way, knowing how the drug works is important in predicting side effects.

Alkylating agents: Alkylating agents are electrophiles or electrophilic reagents, attacked by the ability of electron rich nucleophilic DNA bases. The majority alkylating agents are bipolar, and they contain two alkyl groups capable of reacting with DNA, and they stop tumor growth by cross-linking guanine nucleobases in DNA double-helix strands-directly attacking DNA. Alkylating agents directly damage DNA to prevent the cancer cell from reproducing. As a class of drugs, these agents are not phase specific; in other words, they work in all phases of the cell cycle. Alkylating agents are used to treat many different cancers, including leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma, as well as cancers of the lung, breast, and ovary.

DNA Intercalators: Intercalator is a remarkable binding process that occurs between double helical DNA and molecules that have relatively flat polycyclic areas. In the intercalation process the deoxyribose phosphate backbone of the helix unwinds partially to form a separation between adjacent base pairs. Then intercalating agents move into this separation and binds to the base pairs above and below by Van der Waal and other non-covalent forces. Additional binding can occur between the non-intercalated portion of the drug and the DNA outer surface. Some of the most important antitumor drugs such as adriamycin, chloroquine and pyrrolobenzodiazepines exert their cytotoxic effects through DNA intercalation [80-82].

DNA Topoisomerase Inhibitors: These drugs interfere with enzymes called topoisomerases, which help to separate the strands of DNA so that they can be copied. They are used to treat certain leukaemia, as well as lung, ovarian, gastrointestinal, and other cancers. Topoisomerases (type I, type II) are enzymes that act on the topology of DNA [83-86] and make it difficult to separate.

Groove binders: Drugs that bind to DNA may occur on the major groove face, minor groove face or a combination. The grooves are excellent sites for sequence specific recognition since there are many potential hydrogen bond donor and acceptor atoms unique to each base pair combination along the base edges. The greater width associated with the B-DNA major groove makes the major groove somewhat more preferable binding groove. Distamycin and Netropsin are naturally-occurring minor groove binders.

1.4 Diabetes

Diabetes mellitus (often referred as diabetes) is a group of metabolic diseases characterized by abnormally high levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test [87]. The World Health Organization recognizes mainly two distinct clinical forms of diabetes, for example, type 1 and 2 [88]. Type 1 diabetes, also known as insulin-dependent or juvenile onset diabetes is usually diagnosed in children and young adults, and is caused by the destruction of the insulin-producing beta cells of the Islets of Langerhans in the pancreas, leading to a deficiency of insulin. Type 2 or non-insulin-dependent diabetes mellitus is the most common form of diabetes and is primarily characterized by insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion and hyperglycemia [89- 90]. Type 2 diabetes mellitus (T2DM) is a growing metabolic disorder, which is expected to affect 366 million people worldwide, by 2030 [91].

1.4.1 Dipeptidyl Peptidase-IV (DPP-4): DPP-4/CD26 is a cell-surface protease belonging to the prolyloligopeptidase family. DPP-4 was first reported in1966 as glycyl-prolyl-β-naphthylamidase and later named dipeptidyl peptidase-4, as recommended by the Enzyme Commission [92]. In the 1970s, the enzyme served initially as a model protein for the study of the catalytic mechanism of serine peptidases and for the investigation of the specifics of proline peptide bonds. In the 1980s, the potential of the enzyme to convert bioactive peptides was discovered, which intensified the search for its function. In the middle of the 1990s, the involvement of DPP-4 in metabolism and the regulation of the cytokines, chemokines and different peptide hormones triggered programs for the development of DPP-4 inhibitors [93]. First patent application for the use of DPP-4 inhibition in the reduction of blood glucose was reported in treatment of Type-2 diabetes [94]. Cross-linking and analytical ultracentrifugation studies have shown that human DPP-4 exists as a dimer and it has been proposed that homodimerization of DPP-4 is essential for its serine protease activity [95-96]. Dipeptidyl peptidase-4 exhibits a strong preference for peptides with proline (Pro) or alanine (Ala) as the penultimate (P1) amino acid, but it is now established that it can also act efficiently on peptides with N-terminal consisting of Xaa-Serine (Ser) [97] and with less efficient cleavage of hydroxyproline, dehydroxyproline, glycine, valine, threonine or leucine at P1 [98-101].

Currently, dipeptidyl peptidase-IV (DPP-4) has been validated as one of the most effective targets for type-2 Diabetes Mellitus (T2DM) treatment. DPP-4 is a serine peptidase, which rapidly inactivates endogenous glucagon-like peptide-1 (GLP-1) with a very short half-life of 1-2 min (**Fig-1.7**) [102-103].

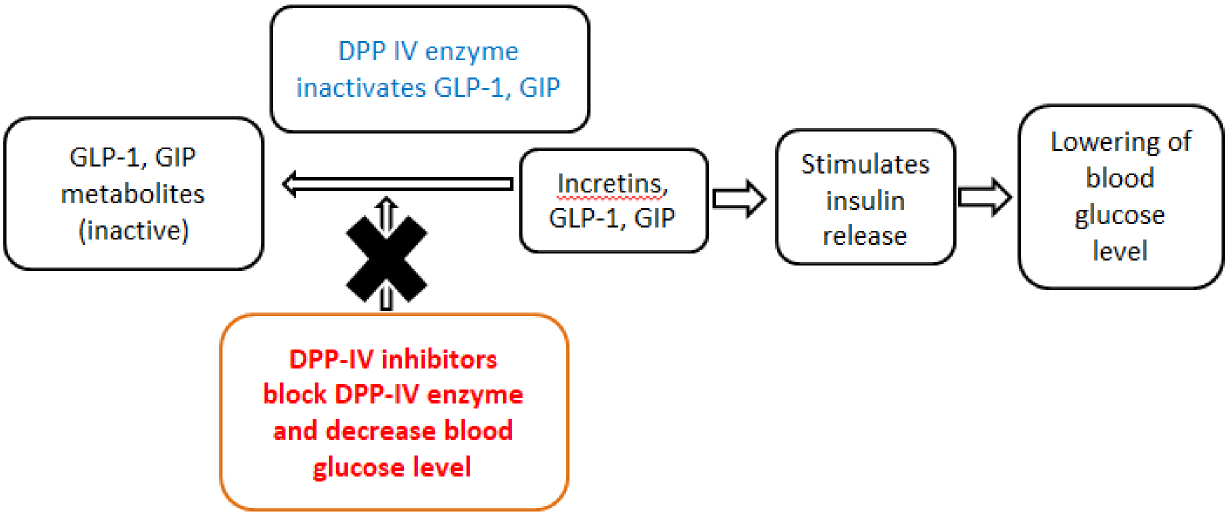


Figure-1.7 Role of DPP-IV enzyme

GLP-1 secreted by intestinal endocrine cells in response to the presence of nutrients can increase the production and release of insulin from pancreatic β cells [104-105]. Administration of GLP-1 reduces the rate of gastric emptying, suppresses appetite and, importantly, promotes β-cell mass [106]. Inhibition of DPP-4 can prevent the degradation of GLP-1, GIP and thus enhance insulin secretion and improve glucose tolerance (**Fig-1.7**) [107]. Various DPP-4 inhibitors, such as Vildagliptin and Saxagliptin (**Fig-1.8**), have already been released as therapeutic drugs for T2DM [108].

1 LAF 237 Vildagliptin

2 BMS 477118 Saxagliptin

Figure-1.8 Pyrrolidine derivatives as DPP-4 inhibitor

DPP-IV is associated with glucose metabolism, immune regulation, signal transduction and apoptosis and regulating cancer. Compounds containing proline ring have been reported as potent DPP-IV inhibitors [109-110]. In diabetic patients, cancer may be favoured by two types of mechanisms: (i) general mechanisms that promote cancer initiation or progression in any organ due to hyperglycemia, hyper insulinemia or drugs that affect all tissues, (ii) site-specific mechanisms affecting cancerogenesis of a particular organ [111]. Thus, it is necessity to develop novel DPP-IV inhibitors with greater safety and fewer side effects.

1.5 Liquid Crystals

Liquid crystals are state of matter between crystalline solid and liquid, which has characteristics of fluid-like behaviour and long range orientational order. Physical properties and mesomorphic state of liquid crystal depends on molecular arrangements (**Fig-1.9**). Change in the molecular geometry enables considerable change in its mesomorphic properties [112]. Liquid Crystal (LC) is multidisciplinary field where all the material science and technology contributes to give excellent and elevated outcome.

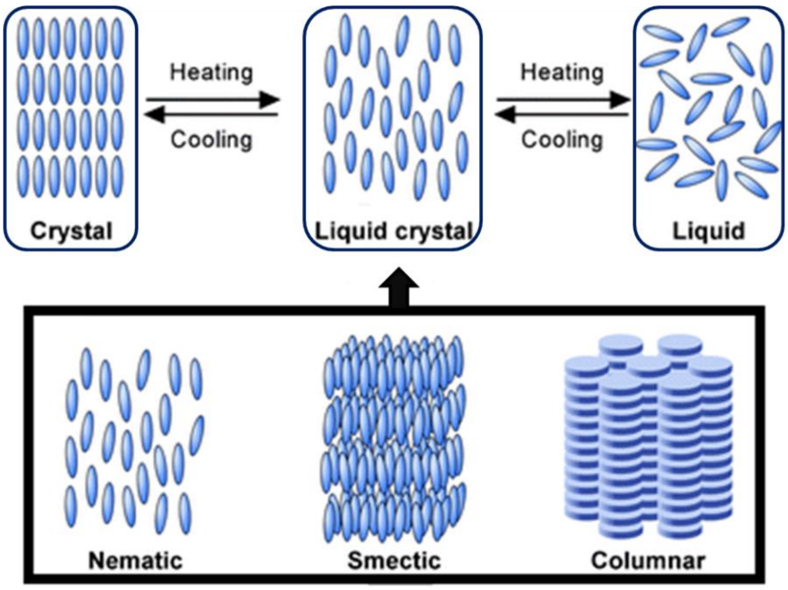


Figure-1.9 Liquid crystal phase transition and different phases

The advent of liquid crystals (LC) in the field of display device technology and other engineering applications lead the researchers all over the globe to work on the platform which in particular focuses on the commercial exploitation of these soft condensed materials.

The phenomenon of liquid crystallinity is known since the early observations by Reinitzer in 1888. He found a phenomenon of "double melting" in cholesteryl benzoate [113]. On heating this ester at 145.5°C it melt from solid to opaque liquid exhibiting vivid colours, which on further heating at 178.5 °C turned into an optically clear liquid. However Lehman was first to make a systematic study of such substances by polarizing microscope with a stage on which he could precisely control the temperature of his samples [114]. He first referred to them as soft crystals; later he used the term crystalline fluids but when he became more convinced that the opaque phase has sharing properties of both liquid and solids, he began to call them as liquid crystal. Friedel has classified liquid crystal mesophase in three broad classifications as smectic, nematic and cholesteric (**Fig-1.9**) [115]. Friedel et al proposed the term 'mesomorphic state' as this phase is an intermediate of a crystalline solid and an isotropic liquid [116]. Often the cholesteric phase is described separately but it is also known as a twisted nematic mesophase.

1.5.1 Properties of Liquid Crystals

Liquid crystal phases are generally cloudy in appearance, which means that they scatter light in much the same way as colloids such as milk. This light scattering is a consequence of fluctuating regions of non-uniformity as small groups of molecules form and disperses. These phases are called as nematic phase or smectic phase as shown in **Fig-1.10** Liquid crystals, like all other kinds of matter, are subject to thermal expansion. As the temperature rises, the average spacing between the aligned molecules of a nematic phase (**Fig-1.10**) increases, thus causes the extraordinary-ray to be increasingly retarded with respect to the ordinary-ray.

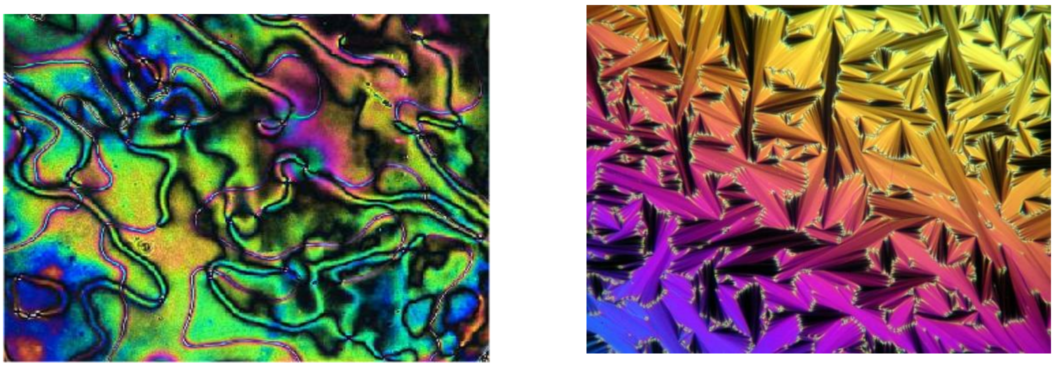


Figure-1.10 (a) Nematic phase (b) focal conic fan texture for smectic A of liquid crystal.

1.5.2 Types of Liquid Crystals

Liquid crystals (LCs) can be divided into thermotropic, lyotropic and metallotropic phases. Thermotropic and lyotropic liquid crystals consist mostly of organic molecules, although a few minerals are also known. Thermotropic LCs exhibit a phase transition into the liquid-crystal phase as temperature is changed. Lyotropic LCs exhibit phase transitions as a function of both temperature and concentration of the liquid-crystal molecules in a solvent (typically water). Metallotropic LCs are composed of both organic and inorganic molecules; their liquid-crystal transition depends not only on temperature and concentration, but also on the inorganic-organic composition ratio [117].

Thermotropic phases are those that occur in a certain temperature range. If the temperature rise is too high, thermal motion will destroy the delicate cooperative ordering of the LC phase, pushing the material into a conventional isotropic liquid phase. At too low temperature, most LC materials will form a conventional crystal [118]**.** Many thermotropic LCs exhibit a variety of phases as temperature is changed. For instance, on heating a particular type of LC molecule (called mesogen) may exhibit various smectic phases followed by the nematic phase and finally the isotropic phase as temperature is increased The essential requirement for a molecule to be a thermotropic LC is a structure consisting of a central rigid core (often aromatic) and a flexible peripheral moiety (generally aliphatic groups). This structural requirement leads to two general classes of LCs: calamitic LCs and discotic LCs.

1.5.3 Liquid Crystal Phases

Liquid crystals (LCs) are matter in a state which has properties between those of conventional liquids and those of solid crystals. For instance, a liquid crystal may flow like a liquid, but its molecules may be oriented in a crystal-like way. There are many different types of liquid-crystal phases, which can be distinguished by their different optical properties (such as birefringence). When viewed under a microscope using a polarized light source, different liquid crystal phases usually appear with distinct textures. The contrasting areas in the textures correspond to domains where the liquid-crystal molecules are oriented in different directions. Within a domain, however, the molecules are well ordered. LC materials may not always be in a liquid-crystal phase (just as water may turn into ice or steam). Thermotropic Liquid crystal systems can be classified in many ways. The mobility in these systems is provided by large amplitude motions of molecules or molecular parts, mainly the flexible chains.

Nematic Phase

One of the most common LC phases is the nematic. The word nematic comes from (Greek: nema), which means "thread". This term originates from the thread-like topological defects observed in nematics, which are formally called 'disclinations'. Nematics also exhibit so-called "hedgehog" topological defects. In a nematic phase, the calamitic or rod-shaped organic molecules have no positional order, but they get self-aligned to have long-range directional order with their long axes roughly parallel [119]. Thus, the molecules are free to flow and their center of mass positions are randomly distributed as in a liquid, but still maintain their long-range directional order. Nematics have fluidity similar to that of ordinary (isotropic) liquids but they can be easily aligned by an external magnetic or electric field. Aligned nematics have the optical properties of uniaxial crystals and this makes them extremely useful in liquid-crystal displays (LCD). Owing to their polarity, the alignment of the rod-like molecules can be controlled by applying an an external magnetic or electric field; this is the physical basis for liquid crystal displays and certain other electrooptic devices.

Smectic Phase

In smectic ("soap-like") phases the molecules are arranged in layers, with the long molecular axes approximately perpendicular to the laminar planes. The only long-range order extends along this axis, with the result that individual layers can slip over each other (hence the "soap-like" nature) in a manner similar to that observed in graphite. Within a layer there is a certain amount of short-range order [120]. The smectic phases, which are found at lower temperatures than the nematic, form well defined layers that can slide over one another in a manner similar to that of soap. In the Smectic A phase, the molecules are oriented along the layer normal, while in the Smectic C phase they are tilted away from it. These phases are liquid-like within the layers. There are many different smectic phases, all characterized by different types and degrees of positional and orientational order [120].

1.5.4 Laboratory analysis of Mesophases

Thermotropic mesophases are detected and characterized by two major methods, the original method was use of thermal optical microscopy, in which a small sample of the material was placed between two crossed polarizers; the sample was then heated and cooled. As the isotropic phase would not significantly affect the polarization of the light, it would appear very dark, whereas the crystal and liquid crystal phases will both polarize the light in a uniform way, leading to brightness and colour gradients. This method allows for the characterization of the particular phase, as the different phases are defined by their particular order, which must be observed. The second method, differential scanning calorimetry (DSC), allows for more precise determination of phase transitions and transition enthalpies. In DSC, a small sample is heated in a way that generates a very precise change in temperature with respect to time. During phase transitions, the heat flow is required to maintain heating or cooling rate change. These changes can be observed and attributed to various phase transitions, such as key liquid crystal transitions [121].

1.5.5 Applications of Liquid Crystals

Examples of liquid crystals can be found both in the natural world and in technological applications. Most contemporary electronic displays use liquid crystals. Lyotropic liquid-crystalline phases are abundant in living systems. For example, many proteins and cell membranes are liquid crystals. Other well-known examples of liquid crystals are solutions of soap and various related detergents, as well as the tobacco mosaic virus, and some clays. The important applications of liquid crystals are Liquid crystal displays (LCDS) [122], Hyperspectral Imaging, Adhesives. [123], Switches and also show medicinal applications [124].

1.6 Summary on Applications carried out on Chromene derivatives.

In this thesis, work on various chromene-2/4-one derivatives with pharmacological applications as well as liquid crystalline properties has been reported. All the chromene derivatives synthesized were studied for different applications. In chapter-2 and chapter-3 study on screening of compounds for anticancer and antidiabetic activity was done. In chapter-4 and chapter-5 compounds synthesized were examined for their liquid crystalline properties.

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