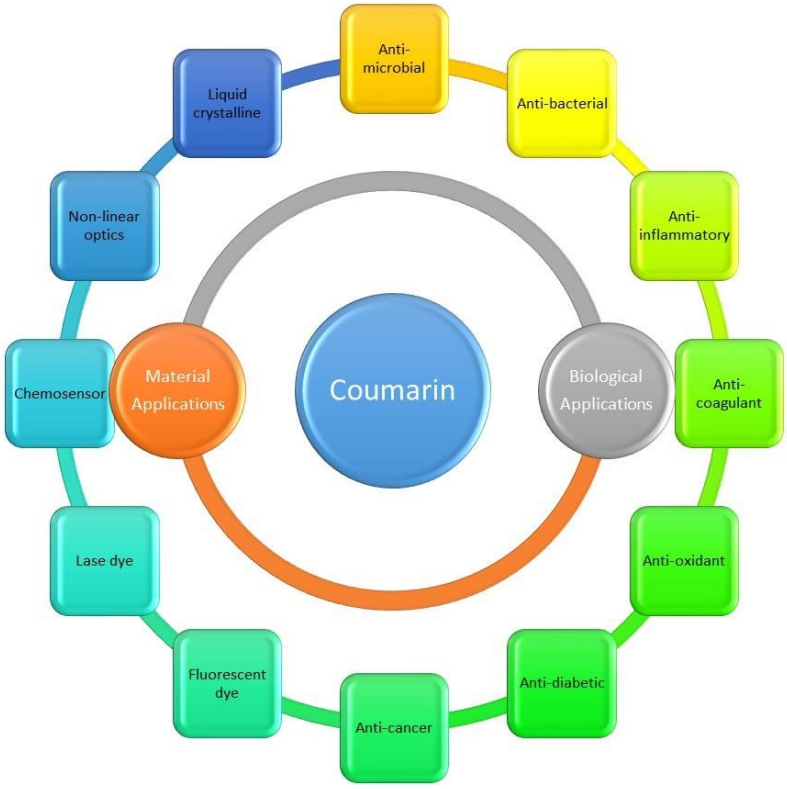
Chapter-1

Introduction to Benzopyran Derivatives and their Applications



1 Introduction

1.1 Coumarin

Coumarin(2H-chromen-2-one) is an oxygen containing and naturally occurring heterocyclic compound that is widespread in the plant kingdom, as well as in certain fungi and bacteria. It included in the benzopyran chemical class and coumarin itself is known for its natural fragrance characteristics. These applications cover wide range of uses, including the fragrance industry, cosmetics production, and the incorporation of industrial additives. Additionally, its derivatives serve as aroma enhancers not only in tobacco but also in specific alcoholic beverages. More than 1300 distinct coumarins have been recognized, originating from various natural sources, with a notable prevalence in green plants [1]. Coumarin is naturally present in a wide array of plants, such as cassia cinnamon, tonka beans, sweet woodruff and lavender. Its role in these plants can vary from acting as a defense mechanism against herbivores to serving as a signaling molecule in ecological interactions.

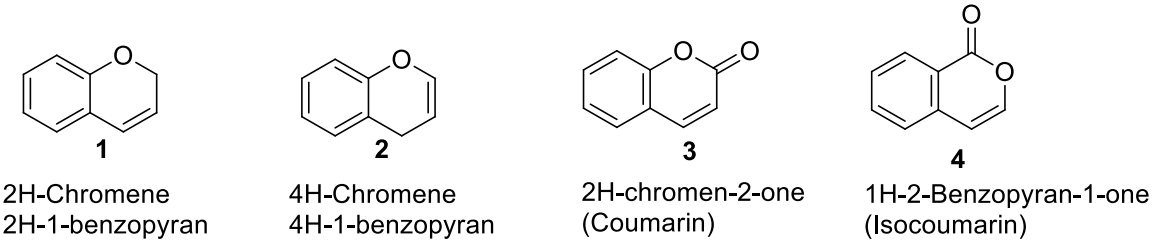


Figure-1.1 Isomers of coumarin **(3-4)**

Coumarin is characterized by its unique chemical structure, consisting of a benzene ring fused to a α-pyrone (2H-1-benzopyran-2-one) ring. This structure imparts its characteristic aroma and contributes to its various chemical properties [2]. What makes coumarin particularly attractive in drug research and development is its advantageous characteristics features of this compound, including its small molecular size, uncomplicated structure, excellent bioavailability, strong organic solvent solubility, minimal toxicity with few side effects, decreased susceptibility to drug resistance, wide-ranging applicability and improved therapeutic outcomes across diverse diseases, have been documented [3]. These qualities, combined with their multifaceted pharmacological effects including anticoagulant [4-5], antimicrobial [6-8], anti-inflammatory [9-10], neuroprotective [11], antidiabetic [12-13], anticonvulsant [14] and anticancer [15-19] properties, position them as promising lead compounds.

The coumarin nucleus is not only naturally abundant but also easily synthesized and adaptable to chemical modification, making it a valuable platform for designing new compounds with

Possible therapeutic uses in the management of different medical conditions. coumarins also find applications in the food industry, where their fungicidal and antioxidant properties are explored and utilized [20]. Furthermore, some benzocoumarins derived from coumarin exhibit anti-algal activity [21].

Isocoumarin has a similar core structure to coumarin but differs in the arrangement of atoms within the molecule [22]. The key difference is the position of the oxygen atom in the ring structure. In coumarin, the oxygen atom is part of the aromatic ring, while in isocoumarin, the oxygen atom is outside the aromatic ring. However, coumarin's most significant contributions are observed in the realms of natural substances, in the field of organic chemistry and the discipline of medicinal chemistry. The extraction, synthesis, and assessment of coumarins have emerged as a rapidly evolving and highly attractive area of study. Isocoumarin and its derivatives find applications in synthetic chemistry as versatile building blocks and have been investigated for potential pharmaceutical uses, including anticoagulant, anti-inflammatory, and antimicrobial properties [23-25]. They also contribute to the flavor and fragrance industry, can be employed in the production of dyes and pigments, hold promise in materials science for applications in organic electronics and polymers [26] and have historical usage in photography as sensitizers and stabilizers, making them multifaceted compounds with diverse applications across various industries. The simplicity and adaptability of the coumarin framework render it a captivating starting point for a wide array of applications. They have been investigated for their role as bioactive agents, supramolecular medicinal drugs, diagnostic agents, pathologic probes, and biological stains [27-29]. Notably, the expansive conjugated system within the coumarin ring, marked by electron-rich and charge-transport properties, plays a pivotal role in its interaction with molecules and ions. This characteristic has led to the rapid growth of coumarin-based ion receptors, fluorescent probes, and biological stains, which find extensive utility in monitoring enzyme activity, complex biological processes, and precise pharmacological and pharmacokinetic properties within living cells [30-31].

Coumarin has demonstrated antitumor activity through several mechanisms. It can inhibit the growth of tumor cells by inducing apoptosis (programmed cell death) and interfering with cell cycle progression, thereby preventing uncontrolled cell proliferation. Additionally, coumarin exhibits antioxidant properties, reducing oxidative stress, which is linked to cancer development. Moreover, some coumarin derivatives have been found to target specific signaling pathways involved in tumor growth and metastasis [32]. These multiple modes of action make coumarin and its derivatives promising candidates for the development of potential

antitumor agents, although further research and clinical studies are needed to fully elucidate their therapeutic potential.

1.1.1 Naturally occurring chromene derivatives which are isolated from plants

Coumarin is present in various plant parts such as roots, stem, leaves, flower, fruit and seeds, although it is typically most abundant in fruits and flowers. Many valuable species that belong to coumarin-rich plant families are commonly used in traditional medicine, for their aromatic properties, and as sources of food for both humans and animals [33]. Within these species, some have a well-established record of biological activity, where coumarins play a role as active constituents. (+)-Calanolide A **5** was initially discovered as the primary potent anti-HIV agent in vitro from the leaves and twigs of the Calophyllum lanigerum tree, gathered in Sarawak, Malaysia, in 1987 [34]. However, subsequent collections of other specimens of the same species yielded only minimal amounts of this compound.

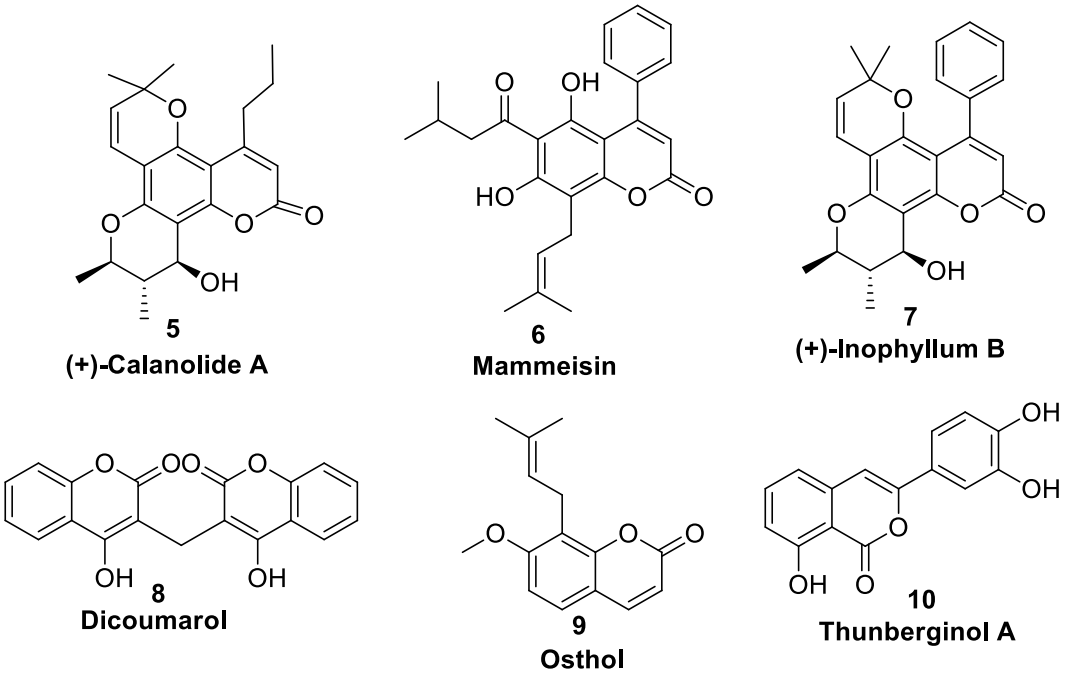


Figure-1.2- Some coumarin derivatives isolated from plants

A comprehensive examination of Calophyllum lanigerum and related species revealed that the latex of Calophyllum teysmanii produced (−)-calanolide B. While (−)-calanolide B is slightly less active than (+)-calanolide A, it possesses the advantage of being readily obtainable from sustainably tapped latex without causing harm to the trees [35]. Mammeisin **6**, a natural derivative of coumarin, was isolated from Kielmeyera elata stems, part of the Clusiaceae family in South America, mainly native to Brazil. This compound exhibits medicinal potential, including antioxidant, antifungal [36] and anti-inflammatory properties [37].

Inophyllum B **7** is a natural compound isolated from certain plants, most notably from the nut of the Tamanu tree (Calophyllum inophyllum). Inophyllum B is part of a group of compounds found in the Tamanu tree's seeds and oil. It is believed to have several potential medicinal properties, including anti-inflammatory, antimicrobial, and wound-healing property. As a result, Tamanu oil and its constituents like Inophyllum B have been used topically for skin conditions, scars, burns and other skin-related issues [38].

Dicoumarol **8** is a naturally occurring chemical compound derived from a combination of plants and fungi. It was first isolated by the research team led by Karl Link at the University of Wisconsin [39]. Dicoumarol has an impact on blood coagulation and was identified in moldy and damp sweet-clover hay as the causative agent of a bleeding disorder observed in cattle and fascinating story of its discovery begins on the prairies of Canada and the Northern Plains of America in the 1920s. Dicoumarol served as the foundational compound for the development of the 4-hydroxycoumarin class of anticoagulant drugs. While dicoumarol was briefly used as a medical anticoagulant, it has been largely replaced since the mid-1950s by its simpler derivative, warfarin and other drugs belonging to the 4-hydroxycoumarin class [40-41]. Osthole, 7-methoxy-8-(3-methyl-2-butenyl) coumarin **9 (Fig. 2.2),** is an ingredient of Traditional Chinese Medicines such as Cnidium monnieri, Angelica pubescens and Peucedanum praeruptorum has been documented to influence a range of signaling pathways, subsequently impacting numerous factors associated with apoptosis, cell cycle control, protein kinases, transcription factors, cytokines, and growth receptors related to conditions such as inflammation, proliferation, and various other health issues [42]. Thunberginol A **10** is an isocoumarin compound that is present in both Hydrangea macrophylla and the herbal product known as hydrangeae dulcis folium, which is made from the leaves of this plant [43].

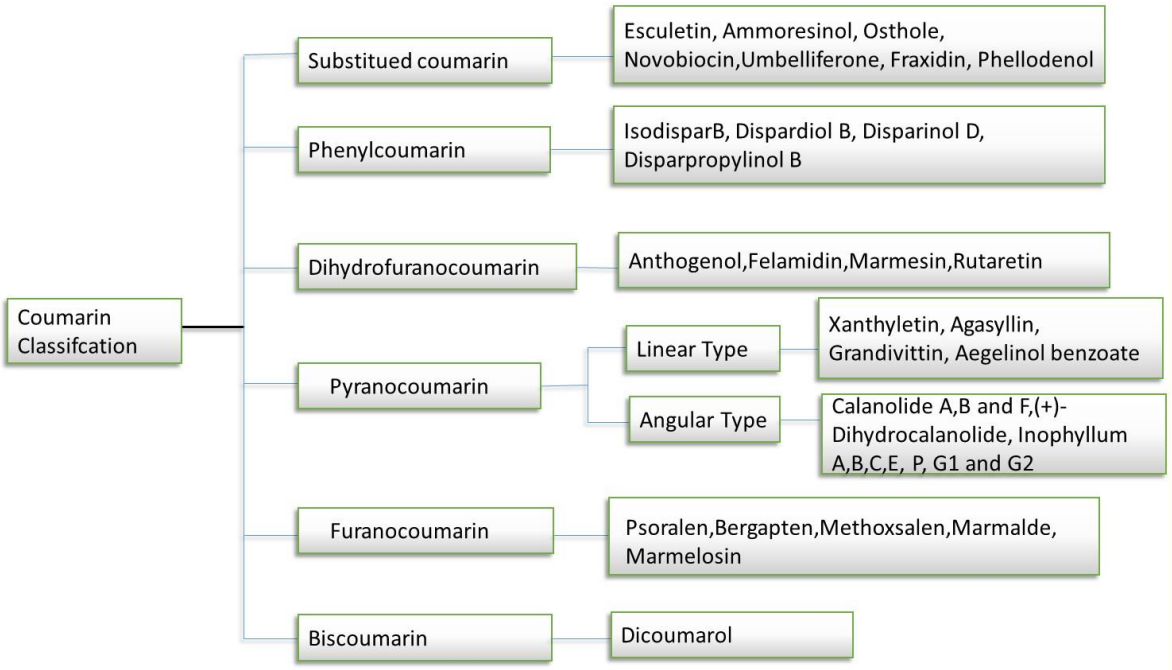


Figure-1.3 Classification of coumarin

Therefore, uncomplicated structure of its chemical foundation, along with the reactivity of the benzene and pyrone rings. The existence of conjugated double bonds contributes to an electronic environment that holds substantial importance within this family of compounds. The presence of conjugated double bonds is responsible for an electronic environment Both naturally existing and artificially synthesized derivatives of chromen-2-one have shown significant interest from scientists because of their wide-ranging characteristics and potential for various biological effects. Numerous drugs, both natural and synthetic, that incorporate the coumarin structure are recognized as established clinical agents.

This underscores the significant fascination with methods for extracting and identifying natural coumarins, as well as the creation of derivatives. Furthermore, the straightforward structure of its chemical foundation is highly appealing, alongside the reactivity of the benzene and pyrone rings. For example, Ulopterol is isolated from plant species which act as an antimicrobial and antifungal properties [44] and also used in the treatment of oedema [45]. Warfarin **11**, a naturally found coumarin compound and a derivative of 4-hydroxy coumarin **Fig-1.4** is obtained from plants such as woodruff and lavender. It is employed as an anticoagulant agent [46]. Ayapin **12** is a natural product found in Dendrobium thyrsiflorum, Pterocaulon virgatum and shows Antitumor activity. Eesculetin **13** also known as Asculetin, 6,7-dihydroxycoumarin and cichorigenin which is abundant in various plants like Sonchus grandifolius and Aesculus turbinatai, in dermatology, the sodium salt of its methyl-derivative finds use in treating varicose veins and also shows good antioxidant properties.

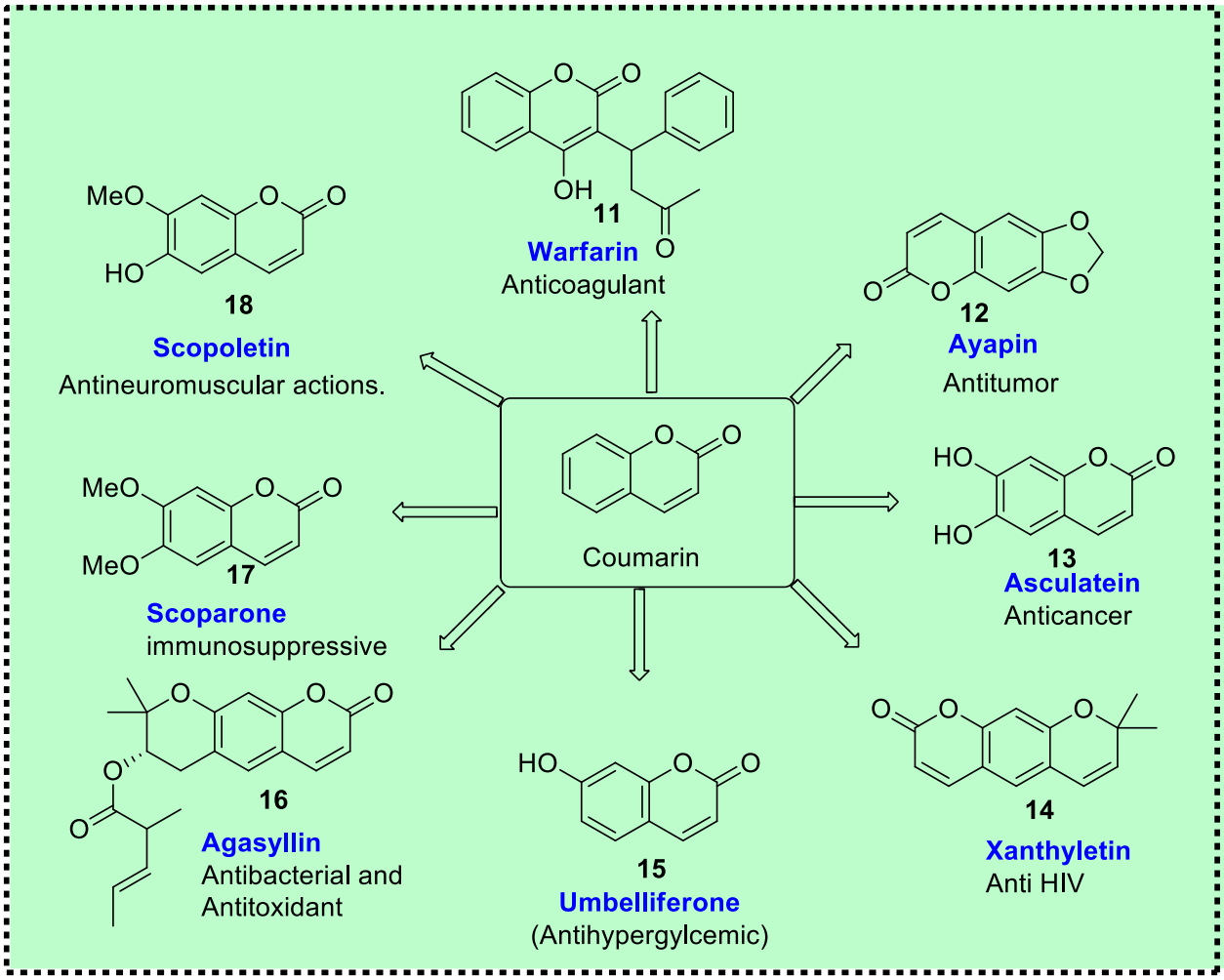
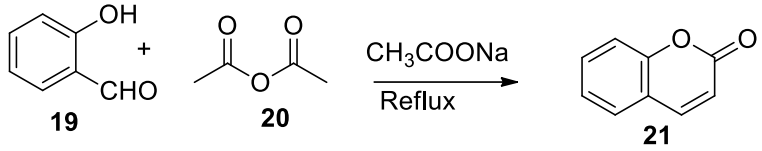


Figure-1.4. Examples of clinically used coumarin derivatives

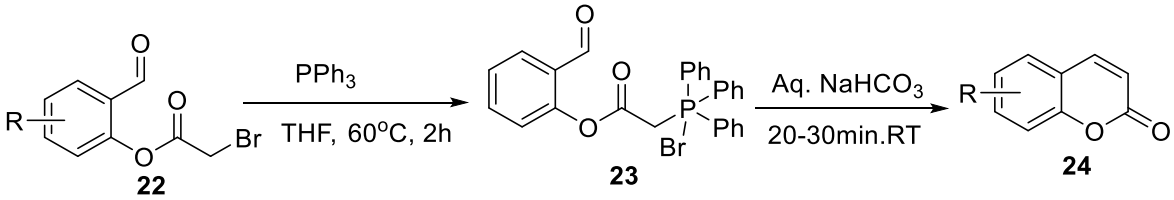
7-Hydroxycoumarin, also known as umbelliferone **15** can be found in various plants, including carrots, coriander, and garden angelica. It has been utilized for multiple purposes, including as a sunscreen ingredient, a fluorescent indicator, and a dye indicator [47-48]. Scopoletin **18** is highly fluorescent when dissolved in DMSO or water and is regularly used as a fluorimetric assay for the detection of hydrogen peroxide in conjunction with horseradish peroxidase. In traditional chinese medicine, it was commonly employed to treat rheumatic arthritis. Scopoletin also possessed strong neuroprotective activity [49].

1.1.2 Different Methods of synthesis of Chromen-2-one Derivatives-

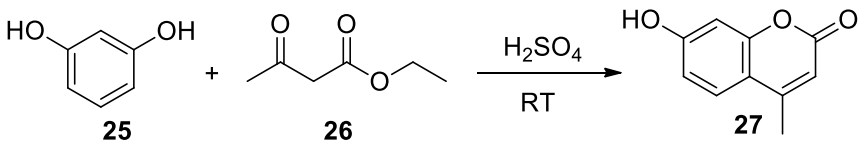
(A) Perkin reaction: Simple unsubstituted coumarin is synthesized by Perkin reaction. Perkin reaction is a classic organic synthesis method used for the preparation of coumarin derivatives. It involves the condensation of an aromatic aldehyde with an acetic anhydride in the presence of a basic catalyst, typically sodium acetate.



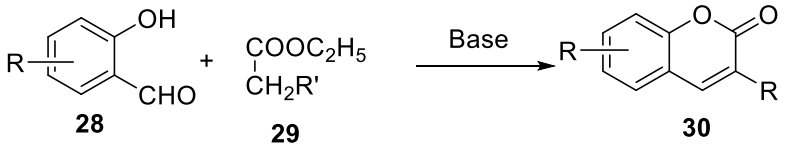
(B) Wittig reaction: The Wittig reaction is known in the literature as one of the most traditional methods for the synthesis of unsubstituted/substituted coumarins Wittig gave synthesis of coumarin with triphenyl phosphine (Wittig reagent), an intermediate formed which subsequently undergoes an intramolecular cyclization reaction, leading to the formation of the coumarin ring system. The Witting reaction is valuable for its efficiency and versatility in creating diverse coumarin derivatives with various substituents for pharmaceutical and chemical applications.



(C) Pechmann condensation: The Pechman condensation is a versatile synthetic method used to produce coumarin derivatives, was applied to synthesis 7-hydroxy-4-methylcoumarin, also known as umbelliferone. This reaction involves the treatment of the starting material i.e. Phenol and ethyl acetoacetate with an acidic condition, such as concentrated sulfuric acid gives good yields of coumarins. The Pechman condensation is a valuable reaction for modifying umbelliferone-derived coumarin structures, allowing for the introduction of various substituents and functional groups, thus expanding the diversity of coumarin derivatives for various applications in pharmaceuticals, materials science and agrochemicals.

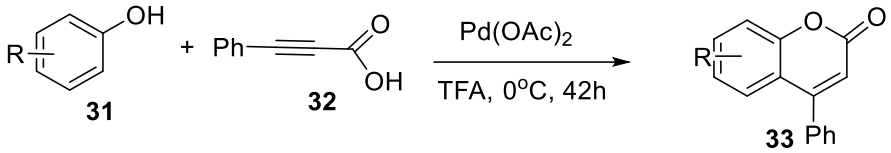


(D) Knoevenagel reaction: Knoevenagel reaction involves the condensation of a benzaldehyde (or related aromatic aldehyde) with carbonyl group containing a compound a, typically malonic acid or its derivatives which contains active methylene group, in the presence of pyrolidine, piperidine, pyridine and other organic bases

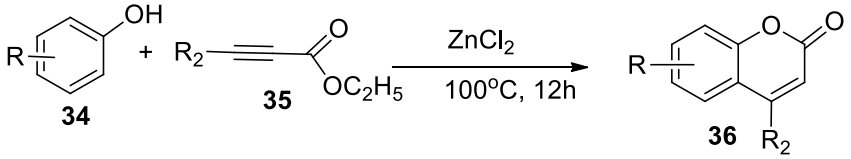


R'= -$COOC_2H_5$, -$COCH_3$

(E) Pd(II)-catalyzed reaction: Unsubstituted and substituted coumarin also synthesized by using Pd(II)-catalyzed reaction of phenol and 3-phenylpropiolic acid in TFA at the cooling condition in presence Palladium(II) acetate $Pd(OAc)_2$ as a catalyst. This method is simple and uncomplicated, making it applicable for synthesizing other coumarins containing electron-rich phenol groups [50].

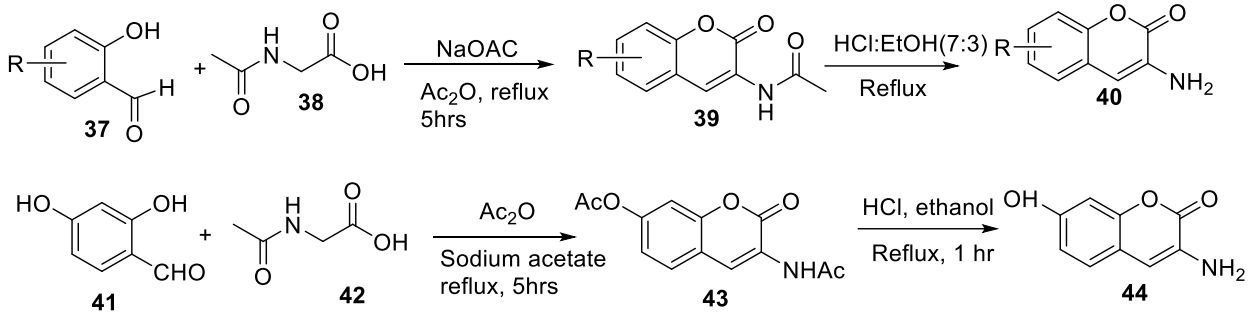


(F) Zn-catalyzed reaction: Synthesis of unsubstituted/substituted coumarin is also possible by using Zn-catalyzed reaction by the reaction of substituted phenols with hydroarylation of acetylenic esters [51].



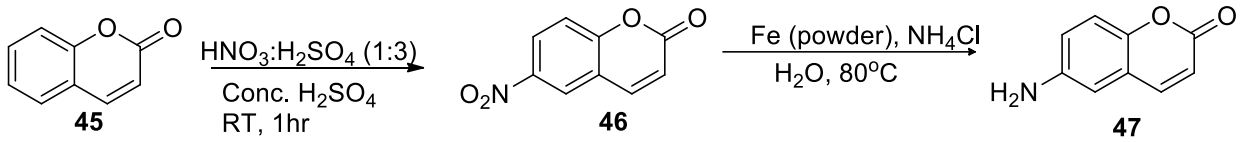
(G) Synthesis of 3-aminocoumarin- 3-Amino chromen-2-one was synthesized through a series of chemical reactions involving the Perkin reaction. Initially, 2-hydroxy benzaldehyde or 2-hydroxy naphthaldehyde was reacted with N-acetyl glycine in the presence of sodium acetate and acetic anhydride. This process yielded 3-acetamido chromen-2-one derivatives. Subsequently, the acetamido group in these derivatives was hydrolyzed using a mixture of ethanol and concentrated hydrochloric acid (in a 7:3 ratio), resulting in the formation of 3-amino-2H-chromen-2-one **40**

Additionally, a similar synthesis route was employed to produce 7-hydroxy 3-amino coumarin **44** starting with resorceraldehyde.



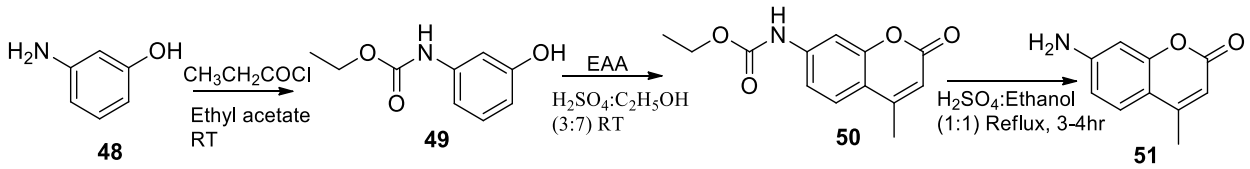
37 38 39 40 41 42 43 44

(H) Synthesis of 6-aminocoumarin: In this method of synthesis first nitration of simple unsubstituted coumarin was carried out by using nitrating mixture (HNO_3:H_2SO_4) in H_2SO_4 gives 6-nitrocoumarin, further reduction was carried out by using iron powdered and NH_4Cl in reflux condition for 2-3 hours give 6-aminocoumarin **47** [52].



45 46 47

(I) Synthesis of 7-amino 4-methylcoumarin: 7-Amino-4-methyl chromen-2-one is synthesized in a three-step process, in which initially use of carbamate-protected 3-aminophenol **49** as the starting material. In the first step, a Pechmann reaction is conducted with ethyl acetoacetate in a 70% ethanolic sulfuric acid, resulting in the formation of 7-carboethoxy amino chromen-2-one **50**. Subsequently, in the second step, deprotection is carried out using a mixture of sulfuric acid and acetic acid in a 1:1 ratio. This deprotection step leads to the desired product, 7-amino-4-methyl chromen-2-one **51** [53].



48 49 50 51

1.1.3 Coumarin Fused or Linked with Other heterocycles

Heterocyclic molecules represent a crucial category of organic compounds, characterized by a ring structure containing at least one heteroatom (e.g., N, S, O, etc.) within the ring. Presently, over 70% of pharmaceutical drugs incorporate a heterocyclic scaffold as a key moiety [54]. The intriguing physiochemical attributes of heterocyclic compounds make them valuable when combined with other organic compounds, enhancing their properties and offering multifunctional activities. The analysis of existing literature demonstrates significant interest in the design and development of heterocyclic molecules fused with coumarin within the

domain of synthetic organic chemistry. Combining coumarin with various heterocyclic compounds featuring different heteroatoms like furan, pyridine, quinoline, pyrazole, benzothiazole, triazine, oxazole, etc., leads to unpredictable activities within these heterocyclic rings, ultimately enhancing the physiochemical properties and biological effects of the coumarin moiety [55]. Consequently, numerous coumarin-fused heterocyclic compounds and their derivatives have been synthesized, and few examples of such structures are depicted in **Fig.-1.5 and Fig.-1.6**

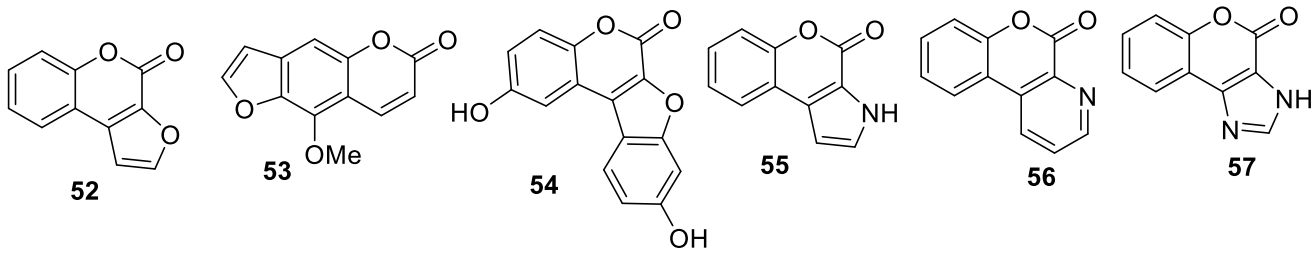


Figure-1.5 Coumarin Fused with Oxygen and Nitrogen containing heterocycles

Coumarin can also be linked or attached to other heterocycles **(Fig.-1.6)** often through chemical reactions that connect their respective functional groups. This approach is commonly used in medicinal chemistry to create compounds with specific pharmacological activities. For example, coumarin can be attached to various heterocyclic rings, such as pyridine or imidazole, pyrazolone, triazole, through linker molecules, yielding hybrids with potential therapeutic applications. These coumarin-heterocycle conjugates often exhibit improved solubility, bioavailability and target specificity, making them valuable candidates in drug discovery and development.

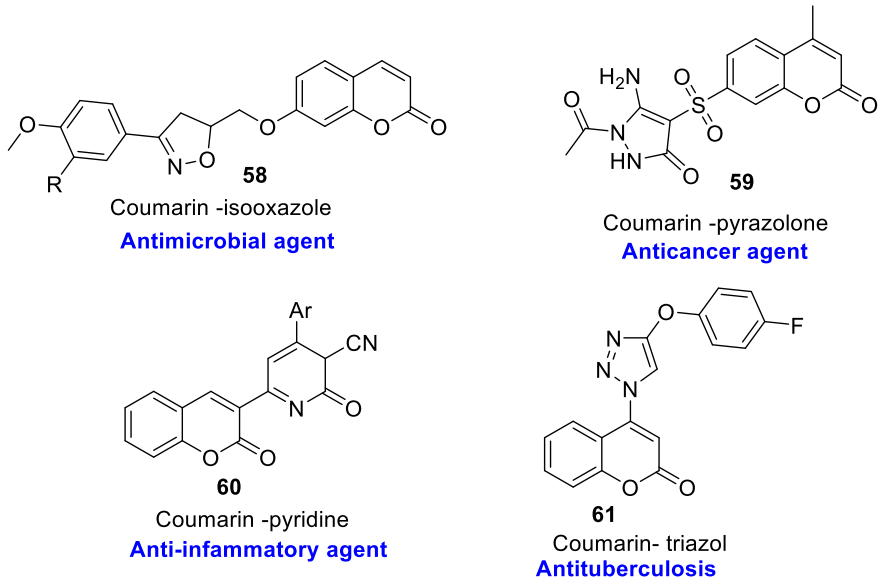


Figure-1.6-Different heterocycles link/attached with coumarin

1.2 Benzofuran

Benzofuran is a heterocyclic compound consisting of a fused benzene and furan ring, which imparts unique chemical properties to it. One of its most significant applications is in the pharmaceutical industry, where benzofuran derivatives serve as key structural motifs in the development of various bioactive compounds [56]. Many benzofuran-containing molecules exhibit diverse pharmacological activities, such as antiviral [57], anti-inflammatory [58] and anticancer [59] properties. Some benzofuran derivatives play a vital role in making medications for mood disorders like depression and anxiety. These medicines, known as serotonin receptor agonists and serotonin-norepinephrine reuptake inhibitors, help treat these conditions [60]. Additionally, benzofuran compounds have found applications in the field of organic synthesis, including in the creation of fragrances, dyes and agrochemicals, making them indispensable building blocks in both medicinal and industrial chemistry [61].

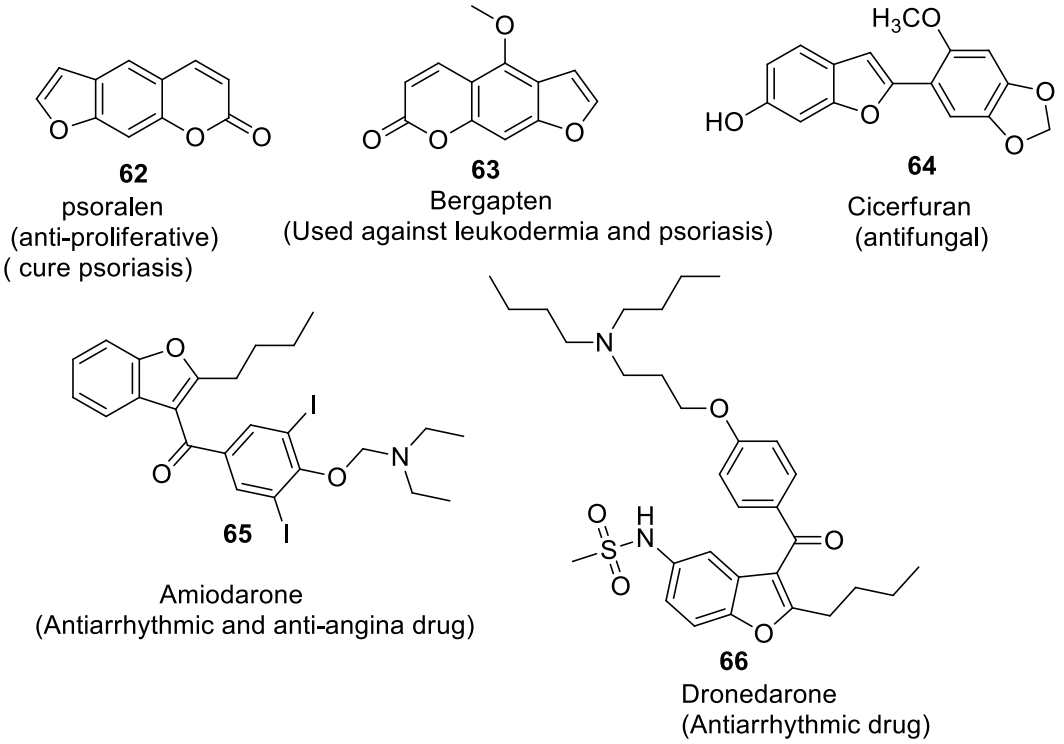


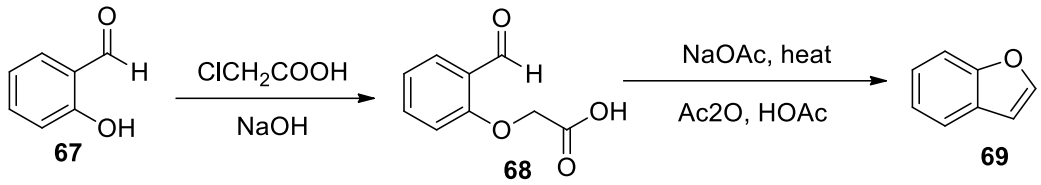
Figure- 1.8 Naturally occurring derivatives containing benzofuran moiety

Some natural benzofuran derivatives are shown in **Fig-1.8** in which Psoralen, a naturally occurring compound found in plants like Psoralea corylifolia and Ammi majus, is well-known for its role in psoralen plus ultraviolet A (PUVA) therapy, which treats skin disorders such as psoriasis and vitiligo by sensitizing the skin to ultraviolet light. Bergapten, or 5-methoxypsoralen, a furanocoumarin in plants like bergamot oranges, is similarly used in conjunction with ultraviolet A (UVA) light for skin conditions. In contrast, dronedarone, a

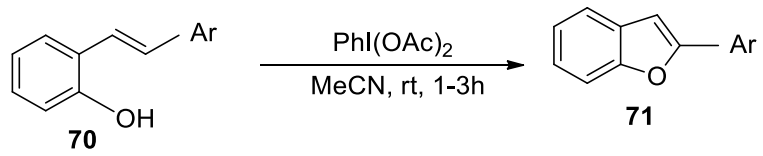
synthetic antiarrhythmic compound, is employed to treat irregular heart rhythms, particularly atrial fibrillation, with fewer side effects compared to its derivative, amiodarone, which is effective but carries risks of thyroid and lung issues. These compounds serve diverse medical purposes, from skin disorder treatment to managing cardiac arrhythmias [62].

1.2.1 Different methods of synthesis of benzofuran:

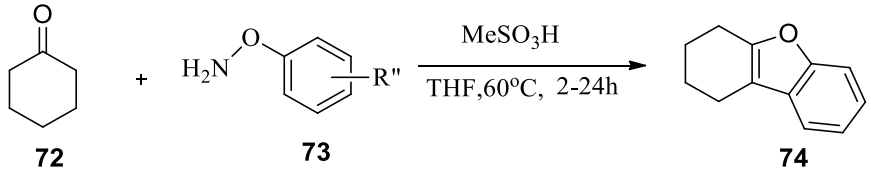
(A) Simple unsubstituted benzofuran was synthesized from reaction salicylaldehyde with chloroacetic acid in water gives o-Formylphenoxyacetic acid. o-Formylphenoxyacetic acid reacts further with sodium acetate and acetic anhydride in glacial acetic acid under reflux condition to give benzofuran.



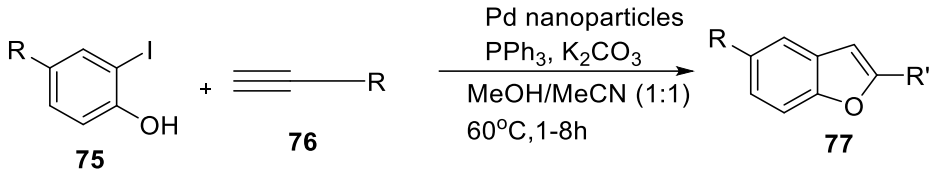
(B) A metal-free cyclization method has been developed to transform ortho-hydroxystilbenes into 2-arylbenzofurans and 2-arylnaphthofurans using iodine-based reagents. When employing (diacetoxyiodo)benzene in an acetonitrile solvent, the desired products can be obtained with high yields [63].



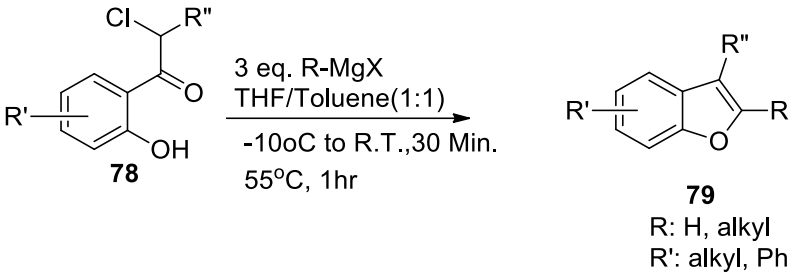
(C) When o-arylhydroxylamine hydrochlorides are subjected to a reaction with cyclic or acyclic ketones in the presence of methanesulfonic acid, a direct formation of benzofuran derivatives occurs through a one-pot condensation-rearrangement-cyclization reaction sequence. This process consistently yields the desired products in good to excellent yields [64].



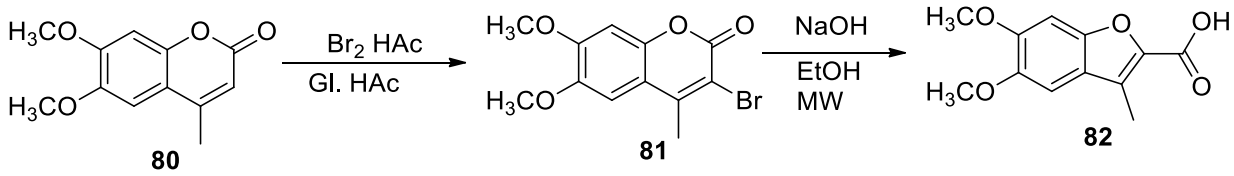
(D) This is one-pot synthesis of various benzofurans via Sonogashira cross-coupling reactions by using palladium nanoparticle under ambient conditions. The catalyst can be recycled and reused without significant loss in its activity [65].



(E) By introducing various Grignard reagents to 1-(2-hydroxyphenyl)-2-chloroethanones, alkoxide intermediates are produced. These intermediates have the capacity to give rise to either 2-substituted benzo[b]furans through a [1,2]-aryl migration process or 3-substituted benzo[b]furans through a direct cyclization and dehydration sequence. A temperature-dependent mechanism involving [1,2]-aryl migration for the formation of 2-substituted benzo[b]furans [66].



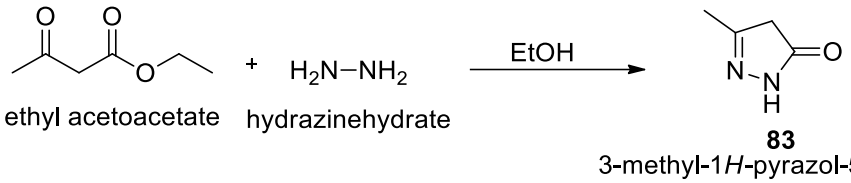
(F) In this synthesis first bromination of coumarin is carried out in presence of glacial acetic acid further cyclization of bromo coumarin done by using NaOH in ethanol gives benzofuran carboxylic acid [67].



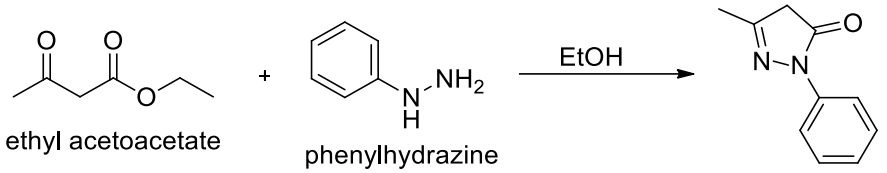
1.3 Pyrazolone

In heterocyclic chemistry pyrazolone derivatives have proven to be a remarkably diverse group of compounds, shows a wide array of biological activities. Pyrazolone is a heterocyclic organic compound characterized by a five-membered ring structure containing three carbon atoms and two nitrogen atoms, with a ketone functional group. This versatile chemical has found applications in diverse fields, including pharmaceuticals and medicinal field. Apart from these medicinal applications of pyrazolone derivatives also used in the dye industry for the synthesis of various dyes [68], often used in conjunction with azo groups to create a subset of azo dyes, occasionally referred to as azopyrazolones and also useful in analytical chemistry as a chelating agent for metal ions. Its unique properties, such as photochemical reactivity, make it of interest in photodynamic therapy and material science, where it has been explored for use in liquid

crystals and organic semiconductors. Ludwig Knorr first reported the synthesis of pyrazolones in 1883 using a condensation reaction involving ethyl acetoacetate and phenylhydrazine which is now famous for knorr pyrazolone synthesis [69].



83
3-methyl-1*H*-pyrazol-5(4*H*)-one



84
3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one

1.3.1 Pyrazolone derivatives with different biological activity:

Pyrazolone is a chemical compound known for its significant applications in the pharmaceutical industry, pyrazolone derivatives have exhibited potent anticancer effects, holding promise in the fight against cancer by inhibiting the growth and proliferation of cancer cells [70]. On another front, certain pyrazolone derivatives have shown efficacy as antifungal agents, effectively combating fungal infections. Moreover, pyrazolone also explored for their antioxidant [71], analgesic and antipyretic properties [72], underscoring their potential for treating a range of medical conditions. The multifaceted biological activities of pyrazolone derivatives underscore their significance in pharmaceutical research, where they continue to play a vital role in the development of innovative therapies and medicines. Many drugs available in the market feature the pyrazolone ring as a crucial structural component. The inclusion of this ring imparts a diverse array of characteristics, including anti-inflammatory, antiviral, antibacterial, antifungal and antiparasitic properties, among others [73].

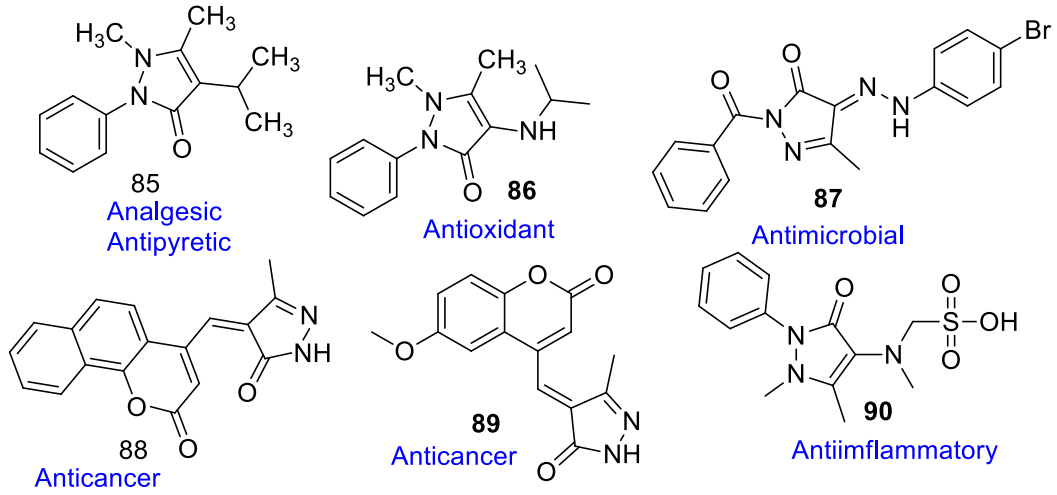


Figure- 1.9-Biologically active pyrazolone derivatives of coumarin

Benzofuran and pyrazolone derivatives have garnered attention in the field of oncology due to their promising anticancer properties. These compounds have demonstrated the ability to interfere with key molecular pathways involved in cancer development and progression. Some benzofuran carboxamide and coumarin pyrazolone derivatives exhibit cytotoxic effects against cancer cells, inhibiting their growth and inducing apoptosis, making them valuable candidates for potential anticancer drugs. Their versatility in targeting different cancer types and significance pathways shows how important they are in the effort to create better treatments for cancer.

1.4 Cancer

Cancer, a multifaceted and formidable health challenge, continues to exert a profound impact on our world today. Based on the most recent data released by the International Agency for Research on Cancer (IARC), there were total of 19.3 million cases and 10 million cancer-related deaths in 2021 [74]. The World Health Organization (WHO) has also highlighted the gravity of the situation, reporting 9.6 million global deaths in 2018 attributable to cancer, equating to one out of every six deaths [75]. Cancer is defined by the uncontrolled proliferation of irregular cells within the body, where old cells fail to undergo programmed cell death, leading to the unchecked formation of new, aberrant cells. This rampant cell growth disrupts normal DNA replication and hinders the secretion of essential proteins by healthy cells. Among the most prevalent cancer types worldwide are lung cancer, cervical cancer, breast cancer and prostate cancer. Recent surveys reveal that breast cancer and lungs cancer were responsible for 1.7 million and 0.5 million deaths, respectively. Notably, female breast cancer stands out as the leading cause of death among women, with one in every four women facing this formidable

disease [76]. While different treatments such as surgery, chemotherapy, and radiotherapy offer significant options for cancer management, they may inadvertently harm healthy cells [77]. Moreover, the number of individuals diagnosed with cancer steadily rises, contributing to the escalating burden of this disease. Characterized by the uncontrolled proliferation of abnormal cells, cancer presents a complex landscape of diverse types and stages, demanding innovative approaches for its understanding, management and treatment [78]. Against this backdrop, it is essential to explore the current state of cancer, the pressing need for effective therapies, and effective methods of cancer treatment have become imperative in the ongoing battle against this challenging situation.

1.4.1 Common way to treat cancer:

Followings are the different ways to treat or controll the cancer [79-80]

Surgery: Surgical removal of tumors and affected tissue is often the primary treatment for localized cancers, aiming to eliminate the cancerous growth.

Radiation Therapy: High-energy X-rays or protons are directed at cancer cells to damage or destroy them, often used in conjunction with surgery or other treatments.

Chemotherapy: Systemic medications are administered to target cancer cells throughout the body. It is particularly useful for cancers that have spread or are difficult to surgically remove.

Immunotherapy: Boosting the body's immune system to recognize and target cancer cells is often referred to as "immunotherapy." This approach aims to enhance the immune response against cancer, aiding in the identification and destruction of cancerous cells. It includes immune checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines.

Targeted Therapy: Medications that specifically target molecules or pathways involved in cancer growth are used to block or inhibit cancer cell proliferation.

Hormone Therapy: For hormone-sensitive cancers like breast and prostate cancer, drugs are used to block the effects of hormones that fuel cancer growth.

Precision Medicine: Genetic profiling of tumors help to identify specific genetic mutations, enabling the selection of treatments tailored to the individual's cancer.

Stem Cell Transplantation: This procedure involves the substitution of damaged bone marrow with viable stem cells, either from the patient (autologous) or a donor (allogeneic).

Clinical Trials: Patients may participate in experimental studies to access cutting-edge therapies and contribute to scientific research.

1.4.2 Diverse Categories of DNA-Interacting Medications

In cancer treatment, variety of drugs are designed to interact with DNA. Drugs used in chemotherapy have diverse mechanisms of action. Among these, alkylating agents, as they are electrophiles attacked by electron-rich nucleophilic DNA bases. like biphasic compounds, directly damage DNA by cross-linking guanine nucleobases, hinders cancer cell reproduction [81]. Remarkably, alkylating agents are not phase-specific, meaning they operate across all stages of the cell cycle. They are employed in treating diverse cancers, including lungs cancer, breast cancer, leukemia, sarcoma as well as ovarian cancers. DNA intercalators represent another significant category of drugs interacting with DNA. This process involves binding interaction between double-helix DNA and molecules that possess mostly planer polycyclic regions [82]. DNA intercalators insert themselves between DNA base pairs, unwinding the helix and binding through non-covalent forces; drugs like Adriamycin and chloroquine achieve cytotoxic effects through intercalation. DNA topoisomerase inhibitors constitute yet another class of drugs that interfere with enzymes known as topoisomerases. DNA topoisomerase inhibitors disrupt enzymes aiding DNA strand separation, used for leukemia, lung, ovarian, and gastrointestinal cancers. Lastly, groove binders are drugs that interact with DNA through its major or minor grooves [83]. These grooves provide optimal locations for recognizing specific sequence due to the numerous potential hydrogen bond donor and acceptor atoms that are unique to each base pair combination along the base edges. Major grooves, with their greater width, are somewhat more preferable binding sites. Naturally-occurring minor groove binders include Distamycin and Netropsin. Mechanisms of interaction between drugs and DNA is essential for tailoring cancer treatments and predicting their outcomes effectively.

1.4.3 Exploring Cell Death: Apoptosis and Necrosis

Cellular demise is a fundamental biological phenomenon that holds significant importance in shaping development, maintenance, and defense of multicellular organisms. It serves as a critical mechanism for removing damaged, unwanted or potentially harmful cells while facilitating tissue remodeling and growth [84]. The regulation of cell death is vital for maintaining tissue homeostasis and ensuring the proper functioning of organs and systems. While there are several forms of cell death, two primary mechanisms that warrant in-depth exploration are apoptosis and necrosis. These two pathways represent clears different approaches to cellular demise, each with distinct features, implications and relevance in health and disease. Roles of apoptosis and necrosis in cellular biology and pathology is discuss below.

1.4.4 Apoptosis

Apoptosis, often referred to as programmed cell death, is an important biological phenomenon crucial for maintaining tissue homeostasis and eliminating damaged or unwanted cells in multicellular organisms. It is characterized by a series of highly regulated biochemical events that lead to cell self-destruction [85]. During apoptosis, Cells undergoes specific structural alterations, such as cell contraction, membrane bulging, nuclear condensation and fragmentation of DNA. These coordinated actions" ensure the controlled elimination of cells without causing inflammation or harm to neighboring cells. Apoptosis plays pivotal roles in various physiological processes, such as embryonic development, immune response regulation, and tissue remodeling, while its dysregulation can contribute to diseases like cancer, autoimmune disorders and neurodegenerative conditions.

1.4.5 Necrosis

Necrosis is a form of cell death that occurs in response to severe damage, toxins, or infection and is characterized by uncontrolled and premature cell demise. Unlike apoptosis, which is a highly regulated and programmed process, necrosis is typically chaotic and uncontrolled. During necrosis, cells swell and burst, leading to the release of cellular contents into the surrounding tissue, often causing inflammation and damage to nearby cells [86]. The consequences of necrosis can be harmful, as it can trigger an inflammatory response and contribute to tissue damage and disease progression. Necrosis is commonly observed in situations such as ischemic injury (lack of blood supply), physical trauma, and certain infections, where the cell's ability to maintain its integrity and undergo a controlled death process is compromised.

1.4.6 Coumarin based anticancer compounds-

Coumarin-based compounds are showing great promising frontier in the search for better ways to fight cancer. With their diverse chemical structures and remarkable biological activities, coumarin derivatives have garnered significant attention in recent years. The therapeutic uses and pharmacological characteristics of coumarin are determined by the way its nucleus is substituted. In recent times, various research studies have documented the creation of new anti-cancer compounds, along with comprehensive investigations into their structure-activity relationships (SAR).

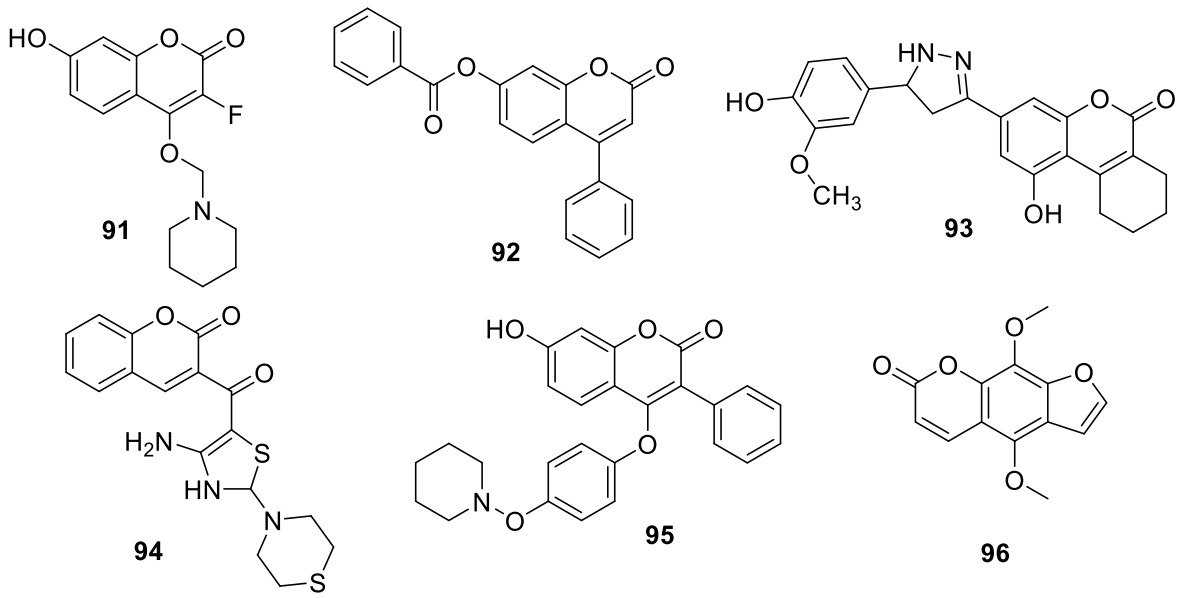


Figure -1.10-Coumarin based anticancer compounds

Their potential to inhibit cancer cell growth, induce apoptosis, and interfere with critical cellular processes has sparked interest in exploring their therapeutic potential against various types of cancer. The literature includes reports on anticancer frameworks derived from coumarin and the corresponding studies on the structure-activity relationships (SAR) of the coumarin moiety. Now, take a closer look at into specific cases where coumarin-based compounds have demonstrated their potential as effective anticancer agents [88-90]. Here are a few notable examples of coumarin based anticancer compounds which are shown in **Fig-1.10**(comp. Nos. **91** to **96**).

Apart from their biological and industrial applications comarin derivatives have found applications in various fields, including, laser dyes, nonlinear optical materials, photosensitive materials and exhibit luminescence due their electron-rich conjugated π-π systems materials. Within the coumarin compounds, studied characteristics such as colour characteristic, luminescence, mesogenic behavior and showed gel formation in both water and organic solvents. These attributes have garnered significant interest as they are seen as potential candidates for the development of next-generation materials, owing to their responsive nature, ecological suitability and energy-efficient processing methods [91-95].

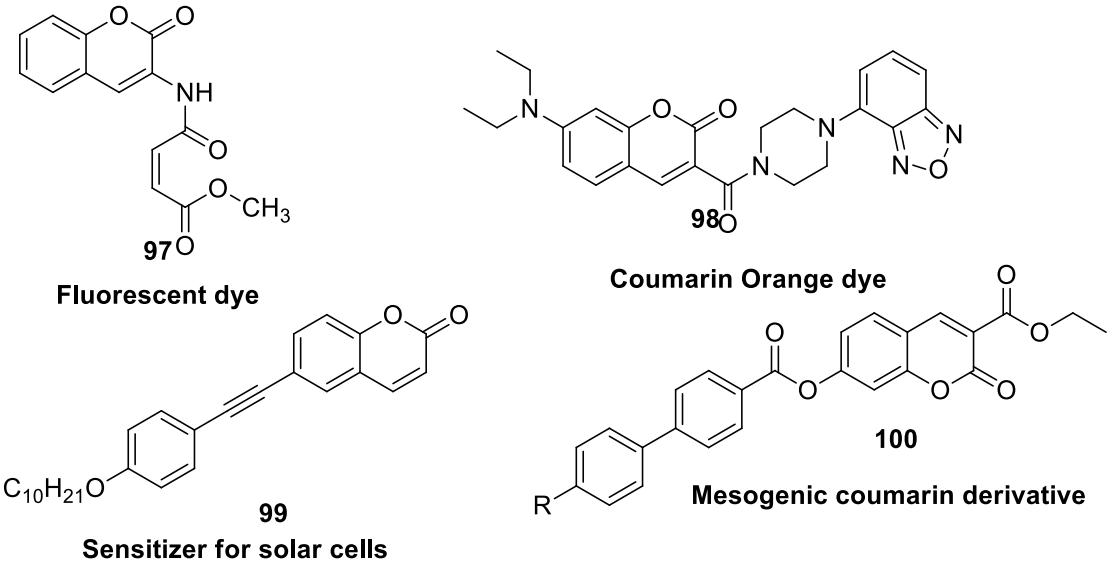


Figure-1.11 Appilcations of coumarin derivatives

Overall, coumarins represent a versatile and valuable class of compounds with a wide range of applications, spanning medicinal chemistry, agrochemicals, the cosmetic and fragrance industry, laser properties, optical properties and also shows the mesogenic behaviour. Mesogenic behaviour means it shows the liquid crystalline properties that contributing significantly to scientific advancements and commercial innovations. Compounds **97 to 100** shows various applications of coumarin derivatives in material chemistry.

1.5 Liquid Crystals

Liquid crystal is a unique state of matter that exhibit both the ordered characteristics of a solid and the fluidity of a liquid. It is composed of organic molecules with elongated shapes, often resembling rods or plates, which align themselves in a specific direction [96]. What makes liquid crystals particularly fascinating is their ability to respond to external stimuli, such as changes in temperature or an electric field, by altering their molecular orientation. This property, known as "liquid crystal phase transition," gives rise to a variety of applications in modern technology, including the liquid crystal displays (LCDs) commonly used in electronic devices like smartphones, televisions and computer monitors. Liquid crystals play a crucial role in these displays because they can selectively manipulate the passage of light based on their orientation, allowing for the creation of vibrant and high-resolution visual displays [97]. Additionally, liquid crystals find applications in other fields, such as materials science, photoelectronics and biotechnology, making them a versatile and indispensable class of materials in today's technological landscape.

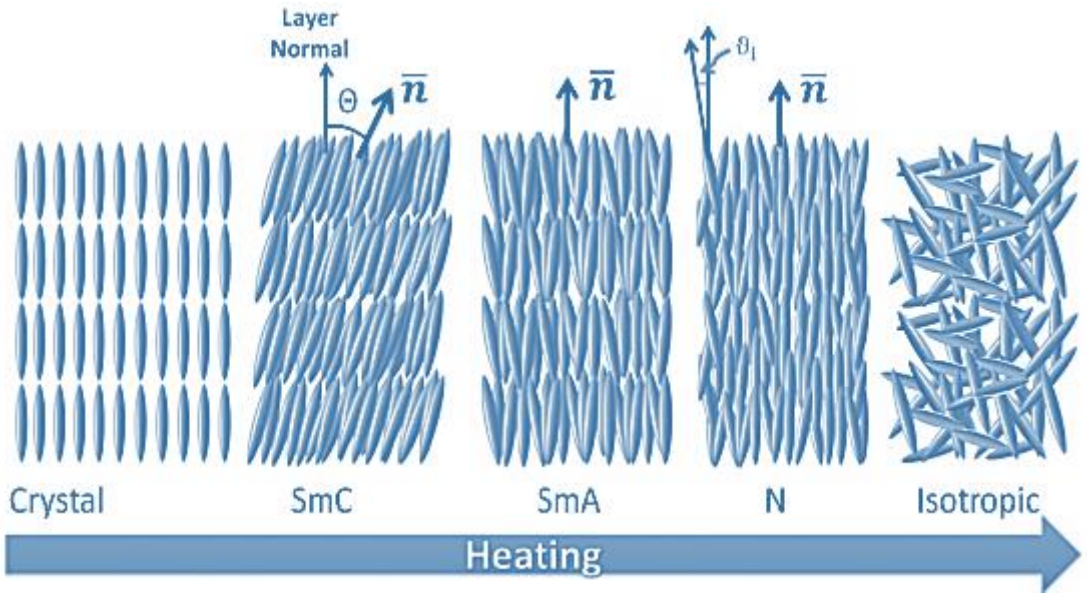


Figure-1.12 Change of liquid crystallization phases on heating

The concept of liquid crystalline compounds has been established since the pioneering observations made by Friedrich Reinitzer in 1888. He made a remarkable discovery involving cholesteryl benzoate, where he noted a fascinating "double melting" phenomenon. At a temperature of 145.5°C, this substance transitioned from a solid state to an opaque liquid, displaying vibrant colors. Upon further heating to 178.5°C, it transformed into a transparent liquid [98]. Otto Lehman later conducted a systematic investigation of such materials, employing a polarizing microscope equipped with a temperature-controlled stage. Initially, Lehman referred to them as "soft crystals," later adopting the word "crystalline fluids." As his understanding deepened, he coined the term "liquid crystal" to describe these substances, recognizing their unique combination of liquid and solid characteristics [99]. Paul Friedel significantly contributed to the classification of liquid crystal mesophases, categorizing them broadly into three main types: smectic, nematic, and cholesteric. The cholesteric phase, often discussed separately, called as a "twisted nematic mesophase." Friedel and his research team introduced the context 'mesomorphic state' to describe this intermediate phase, as it exhibited properties that bridged the gap between crystalline solids and isotropic liquids [100]. These pivotal discoveries laid the groundwork for extensive research and applications of liquid crystals, which have become integral in various fields, including display technology, materials science and optics.

1.5.1 Classification of Liquid Crystals

Liquid crystals, fascinating materials that exhibit properties of both liquids and solids, are classified into several distinct phases based on their molecular arrangement and behavior. Thermotropic liquid crystals change phases with temperature, transitioning between solid-like and liquid-like states. Lyotropic liquid crystals form in solvents, with their properties influenced by solvent concentration [101]. The most common liquid crystal phases include nematic, smectic, cholesteric and discotic phases. In the nematic phase, molecules are loosely aligned, allowing for some directional order while maintaining fluidity. Smectic phases, on the other hand, exhibit layered structures, with molecules arranged in distinct layers that can slide past one another. Cholesteric liquid crystals have a helical or twisted structure, causing them to reflect specific wavelengths of light and exhibit unique optical properties [102]. Discotic phases consist of disc-shaped molecules that form columnar structures. These classifications are crucial for understanding the diverse applications of liquid crystals. **(Fig.-1.13)**

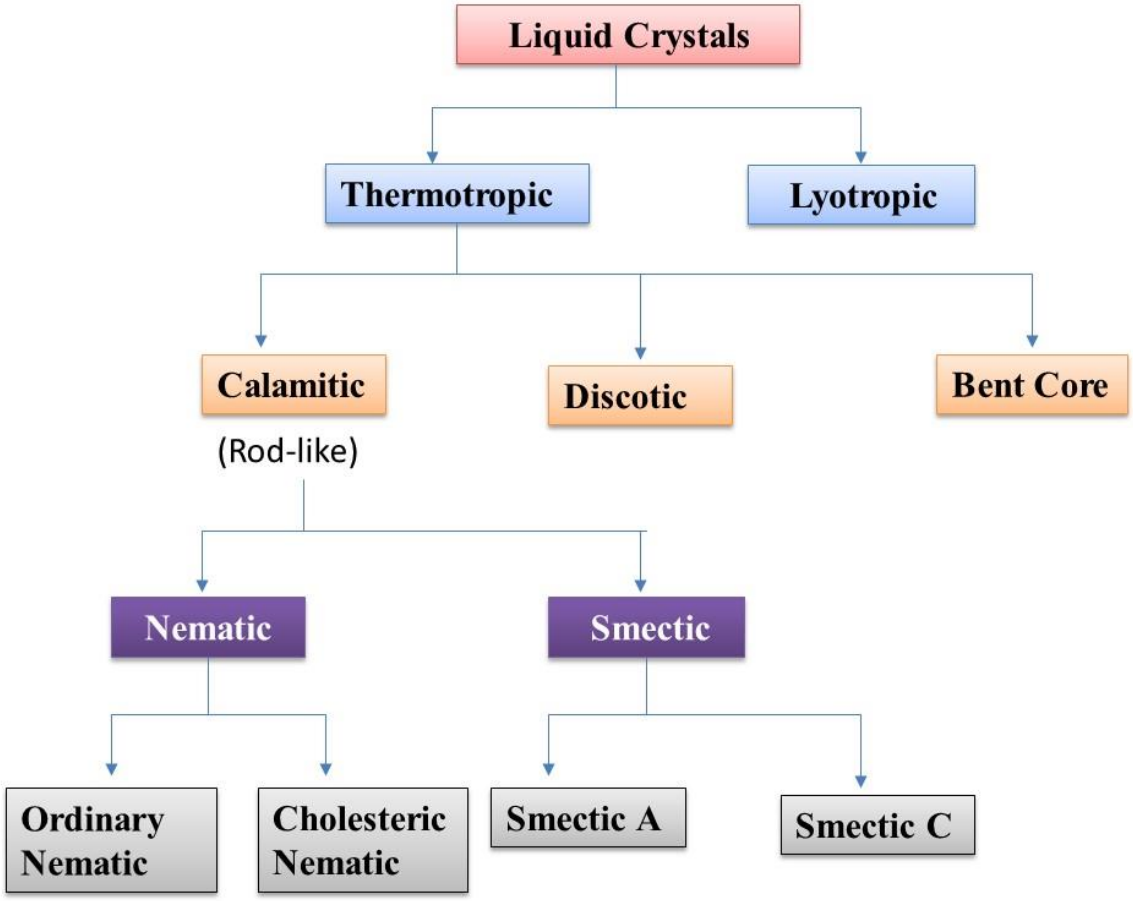


Figure-1.13 Classification of liquid crystal

1.5.1.1 Smectic Mesophase

The smectic mesophase is a fascinating state of matter within the realm of liquid crystals, the term "smectic" originates from term "smēktikos," (Greek) which signifies "soapy" or "like soap" characterized by its distinctive layered molecular arrangement. In this phase, liquid crystal molecules align themselves into well-defined sheets, with their long axes parallel to one another within each layer. While these layers are ordered, there is no regular positional order between adjacent layers [103]. This unique organization imparts intriguing optical and physical properties to smectic liquid crystals, making them valuable in applications such as liquid crystal displays, sensors and optical devices. The layered structure of smectic phases offers a promising platform for the development of advanced technologies in the fields of optics and photonics [104].

1.5.1.2 Nematic Mesophase

Nematic liquid crystals derive their name originates from the term "nema,"(Greek) denotes "thread," which refer to the thread-like. In its general form, a nematic phase is defined by an absence of long-range spatial arrangements but a strong level of orientational order, where the constituent molecules align predominantly in one direction, topological defects, formally known as 'disclinations,' observed within this phase. Additionally, nematics can exhibit "hedgehog" topological defects. In the nematic phase, rod-shaped organic molecules lack positional order but exhibit long-range directional order, with their long axes roughly parallel [105]. This distinctive molecular organization grants nematics the ability to flow like conventional liquids, yet maintain a persistent directional alignment. They can be easily oriented by external magnetic or electric fields due to their polarity, a property crucial in applications such as liquid crystal displays (LCDs). This unique molecular organization gives rise to intriguing optical effects, notably birefringence and serves as a foundation for various scientific investigations into the behavior of nematic liquid crystals under external factors such as electric fields or temperature fluctuations, shedding light on their complex and fascinating properties [106]. **Fig-1.14** shows various phases of liquid crystal.

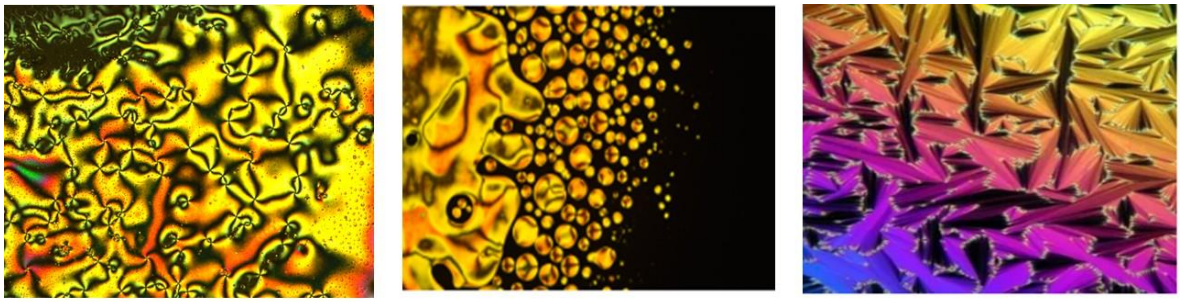


Figure-1.14: Mesomorphic images (a) Nematic schlieren (b) Nematic droplet (c) Smectic A

1.5.2 Structural requirements for liquid crystals

Calamitic liquid crystals are defined by their elongated, rod shape structure, and comprising three main structural elements: Core structure or rigid ring systems, connecting linkage groups and flexible terminal groups

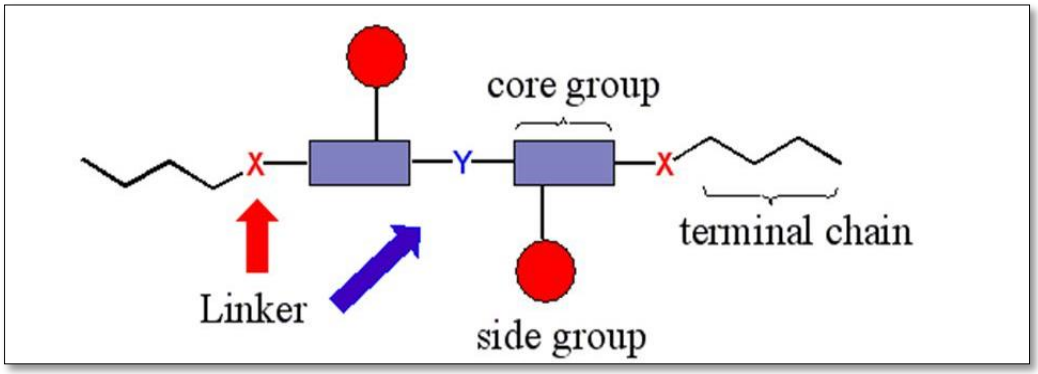
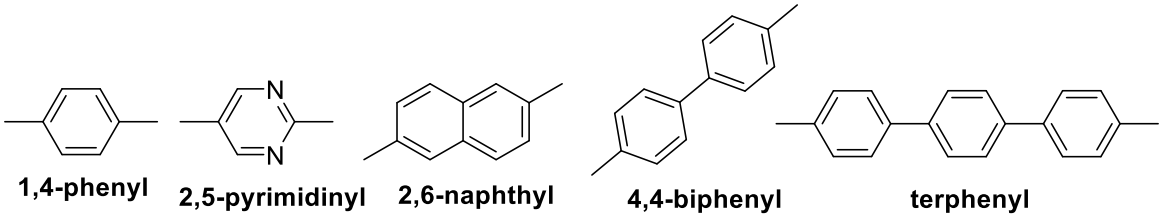


Figure-1.15 Structural requirements for liquid crystals

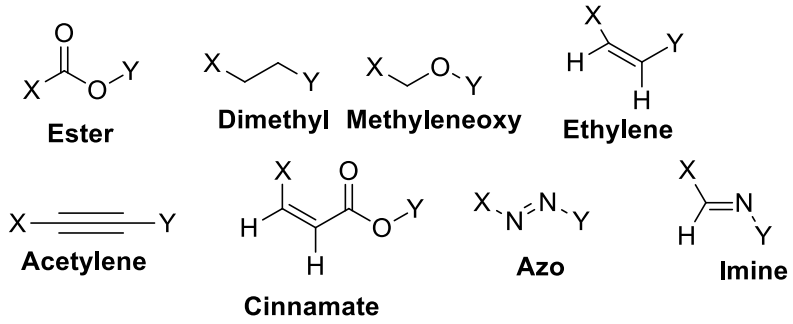
(A) Core structures

The primary requirement for liquid crystalline behavior appears to be an elongated, structurally rigid and greatly anisotropic shape. The core structure of a liquid crystal molecule refers to its central, rigid framework. This core structure often exhibits an elongated or anisotropic shape, which is crucial for liquid crystallinity. The core structure provides the molecule with a degree of longitudinal symmetry, allowing for alignment along a specific axis. Common core structures include benzene rings, cyclohexane rings, or other rigid, planar or elongated structures. The choice of core structure influences the type of liquid crystal phase formed and its properties. Below are few examples of core structures.



(B) Linking groups

Linking groups connect one part of the core to another and also link the terminal chains to the core. It shows crucial part in determining the flexibility and spacing between molecules in the liquid crystalline phase. The linking group can introduce flexibility or stiffness, affecting the overall shape and behavior of the liquid crystal. For example, a flexible alkyl chain linking group can allow for greater molecular motion and flexibility, while a rigid linking group may restrict movement. Below are few examples of linking groups.



(C)Terminal moieties

Terminal moieties are the end groups attached to the linking group. These moieties can be polar or nonpolar and have a significant influence on the total properties of the liquid crystal. For instance, polar terminal groups can introduce dipole moments, making the liquid crystal responsive to external electric fields. The nature of the terminal moieties also influences the intermolecular forces between molecules, affecting the phase transition temperature and stability of the liquid crystalline phase. The usual role of a terminal unit is to stabilize the mesophase and add flexibility to the rigid core structure

i) Alkyl Chain Terminal Moiety: $-OC_nH_{2n+1}$

ii) Fluorinated Terminal Moiety: CF_3 (Trifluoromethyl), C_2F_5 (Pentafluoroethyl)

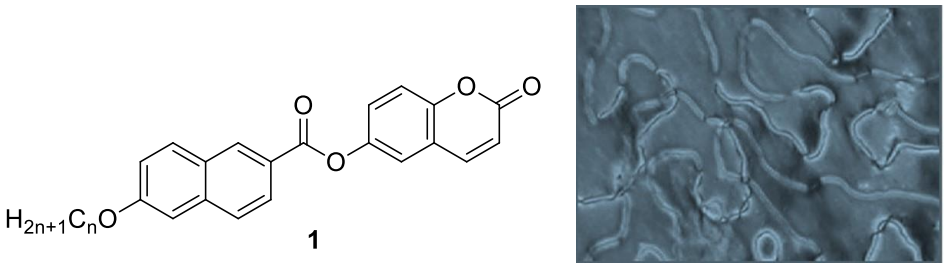
iii) Cyano (CN) Terminal Moiety: CN (Cyano Group)

The core structure provides the molecular shape and symmetry necessary for liquid crystallinity. The linking group connects the core structure to the terminal moieties, determining the molecule's flexibility and spacing. The terminal moieties influence the intermolecular forces and overall properties of the liquid crystal. The precise combination of

these elements in a liquid crystal compound is carefully designed to achieve specific liquid crystal phases and desired properties for various applications.

1.5.3 Coumarin bases liquid crystal compounds

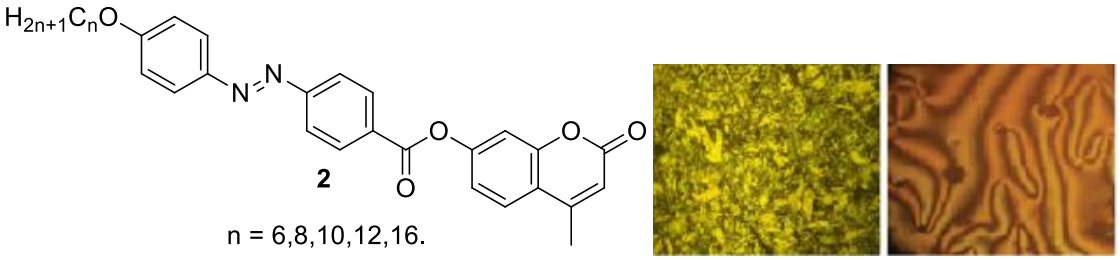
Coumarin ester based derivatives have been synthesized by Morita et al. studied their Physicochemical characteristics. Polar liquid crystal materials containing a coumarin ester based derivative 2-oxo-2H-chromen-6-yl-6-(alkyloxy)-naphthalene-2-carboxylate showed monotropic nematic (N) mesophase [107].



1

(1) Coumarin azo ester

Coumarin derivatives with azo linkages contain ester moiety reported by Ahmed et al, and mesophase study of coumarin esters and its azoesters of 4-methyl-2-oxo-2H-chromen-7-yl 4-(2-(4-alkoxyphenyl)diazenyl) benzoates, which showed smectic C and Nematic mesophase [108].

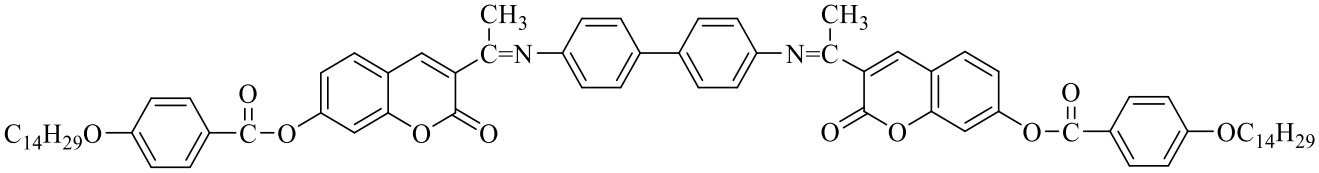


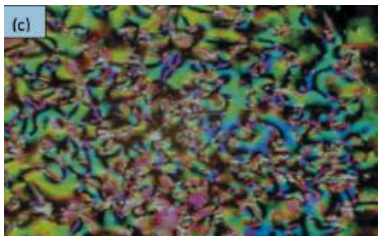
2

n = 6,8,10,12,16.

(2) Dimerization of Coumarin with Benzidine and Phenylenediamine Cores

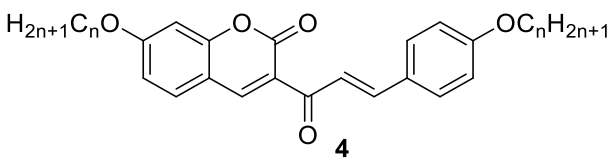
Mohammad et al reported novel series of the symmetrical coumarin dimers consists of two Schiff base moieties as connecting groups and central cores composed of either phenyl or biphenyl moieties originating from coumarin heterocycles have been synthesized and studied for mesomorphic properties [109].





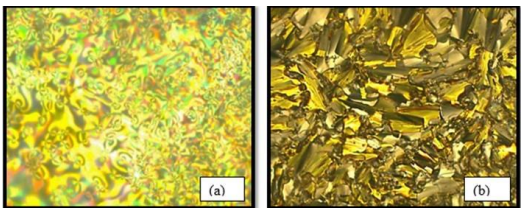
(3) Coumarin chalcone as liquid crystal

Soman et al, synthesized the coumarin chalcone with symmetrical alkoxy chain length and studied mesomorphic properties in which lower substitutes exhibited nematic behaviour while higher substitutes exhibited smectic mesophase [110].



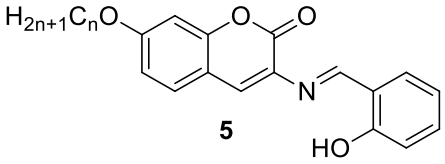
4

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

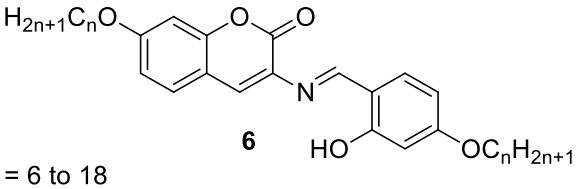


(4) Comarin Schiff base

Very recently novel homologous series of coumarin Schiff base derivatives with alkyloxy chain on coumarin part and with alkyloxy chain on both end of the molecule for mesomorphic behaviour repoeted by Rina et al [111].

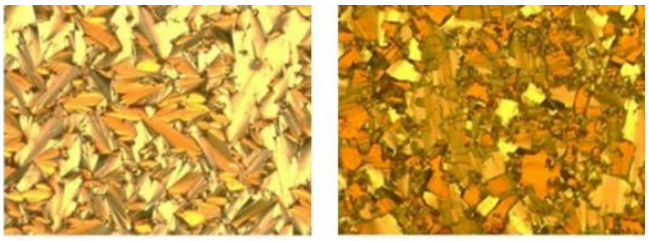


5



6

n = 6 to 18



(a) **(b)**

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