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COUMARINS IN MEDICINAL CHEMISTRY: UNVEILING A PHARMACOLOGICALLY RICH SCAFFOLD

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ABSTRACT

Coumarins are a class of compounds belonging to the benzopyrone family, consisting of a pyrone ring fused to a benzene ring. Benzopyrones are broadly divided into two categories: benzo-α-pyrones, which include coumarins, and benzo-γ-pyrones, which primarily encompass flavonoids. In nature, the three most commonly occurring coumarins are scopoletin, esculetin, and umbelliferone. Their biosynthesis involves precursor compounds such as p-coumaric acid, caffeic acid, and ferulic acid, which undergo a key transformation known as ortho-hydroxylation. Coumarins possess notable medicinal properties, making them valuable scaffolds for structural modification and drug development. They exhibit a wide range of biological activities, including antibacterial, anticancer, and anti-inflammatory effects, which has generated significant interest in exploring their therapeutic potential.

Keywords: Coumarins, Benzopyrones, Benzo-α-pyrones, Umbelliferone, Biosynthesis, Pharmacological properties, Antitumor activity, Bacteriostatic agents

INTRODUCTION-

The chemical class *coumarins* derives its name from "Coumarou," the traditional term for the tonka bean (*Dipteryx odorata* Wild., Fabaceae), from which coumarin was first isolated in 1820 **[1]**. Coumarins are broadly categorized into four structural groups: simple coumarins, furanocoumarins, pyranocoumarins, and pyrone-substituted derivatives. Simple coumarins, including coumarin, 7-hydroxycoumarin, and 6,7-dihydroxycoumarin, comprise hydroxylated, alkoxylated, and alkylated modifications of the parent coumarin scaffold. Furanocoumarins contain a five-membered furan ring fused to the coumarin nucleus, with either linear or angular

substitution patterns depending on the site of fusion. Pyranocoumarins share similar structural features but carry a six-membered pyran ring instead of a furan ring. Pyrone-substituted coumarins, such as 4-hydroxycoumarin, feature alterations on the pyrone moiety **[2]**. Warfarin, a widely used synthetic anticoagulant, belongs to this coumarin class. Although the simple coumarin molecule is often regarded as the parent structure of the benzo-α-pyrone group, 7-hydroxycoumarin is frequently considered the fundamental precursor for the biosynthesis of more complex coumarins **[3]**. Genistein, an isoflavone classified under the benzo-γ-pyrone group, is naturally abundant in soy and has been extensively evaluated for its chemopreventive potential, particularly in hormone-related cancer models **[4,5]**. Coumarins are distributed extensively across the plant kingdom and occur in notably high concentrations in certain essential oils—such as cinnamon bark oil (approximately 7,000 ppm), cassia leaf oil (up to 87,300 ppm), and lavender oil. They also occur in fruits like bilberry and cloudberry, as well as in green tea and foods such as chicory **[6, 7]**. Higher plants, especially those belonging to the Rutaceae and Umbelliferae families, represent the richest botanical sources.

The distribution of coumarins within plants varies, with fruits generally containing the highest levels, followed by roots, stems, and leaves. Environmental and seasonal factors may influence their accumulation. Several new minor coumarins have been isolated from the fruits and stem bark of *Calophyllum dispar* (Clusiaceae), a genus comprising around 200 species used traditionally across tropical regions **[8,9]**. Although higher plants remain the primary sources, certain microbial species also produce coumarin derivatives; aflatoxin from *Aspergillus* spp. and novobiocin and coumermycin from *Streptomyces* spp. are notable examples **[10, 11]**.

Chemical Profile

Structure

Coumarin and its derivatives constitute the major class of orally administered anticoagulant agents. While native coumarin is poorly soluble in water, the introduction of a 4-hydroxy group imparts weak acidic character, enabling these molecules to dissolve under mildly alkaline conditions

The structural features of coumarin and its major derivatives are illustrated below. Warfarin is formulated and marketed in the form of its sodium salt. The molecule contains a single chiral center, and its S (–) enantiomer exhibits approximately 5–8 times greater anticoagulant activity than the R (+) form. Despite this difference in potency, commercially available warfarin is provided as a racemic mixture.

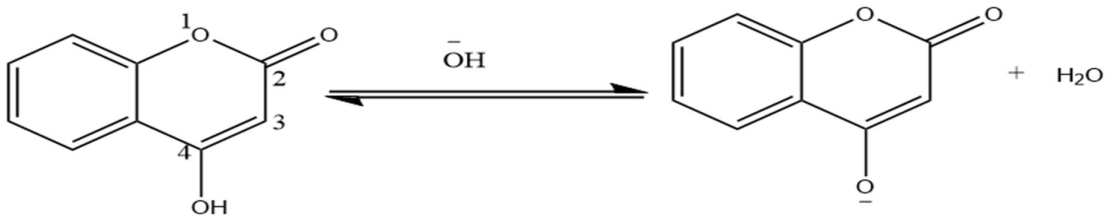
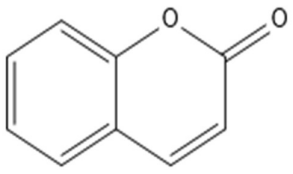


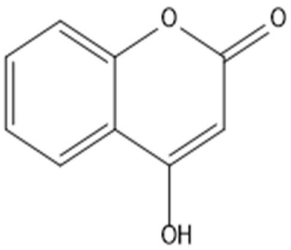
Figure 1.1: Basic derivatives of coumarins

Structure Activity Relationships

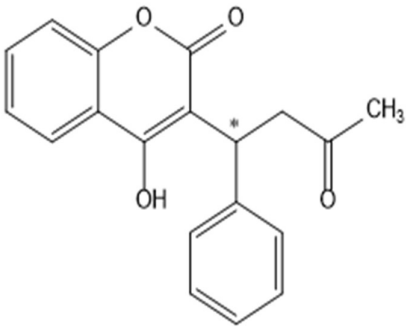
Coumarin and 4-hydroxycoumarin themselves lack intrinsic anticoagulant activity. Link, who first isolated and characterized bis-hydroxycoumarin (dicoumarol) from spoiled sweet clover, demonstrated that three structural features are essential for anticoagulant action: the presence of a 4-hydroxyl group, substitution at the 3-position, and a bis-coumarin framework **[11]**. The benzo-2-pyrone core characteristic of simple coumarins originates biosynthetically from the phenylacrylic backbone of cinnamic acids.



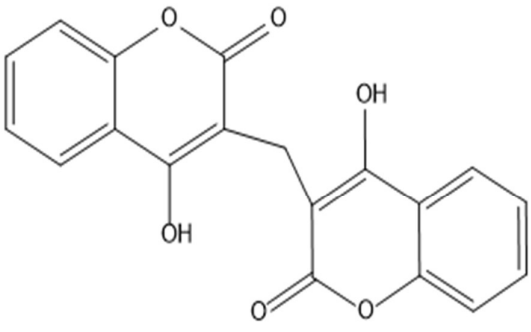
COUMARIN
2*H*-chromen-2-one



4-hydroxy-2*H*-chromen-2-one
4-HYDROXYCOUMARIN



4-hydroxy-3-(3-oxo-1-phenylbutyl)-2*H*-chromen-2-one
WARFARIN
*chiral center



3,3'-methylenebis(4-hydroxy-2*H*-chromen-2-one)
BISHYDROXYCOUMARIN
(Dicoumarol)

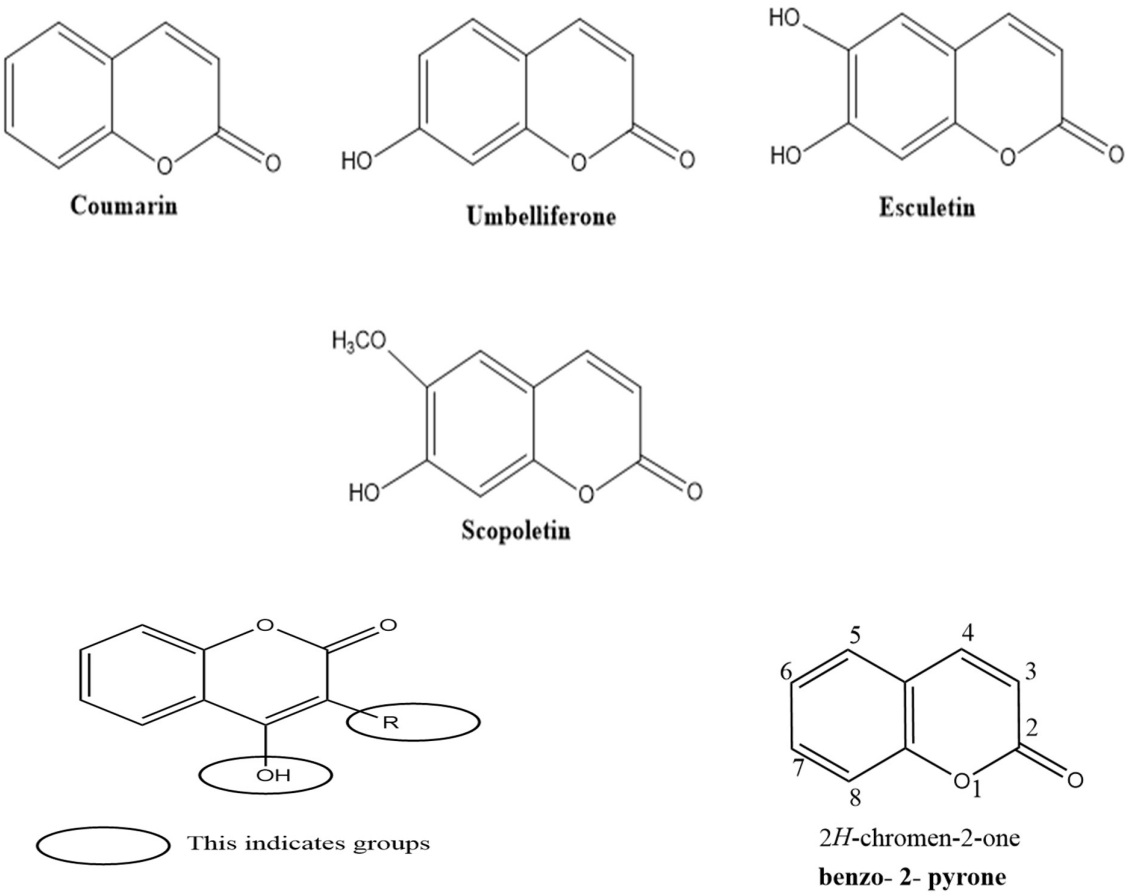


Figure 1.2: Structural activity relationship of coumarins

The coumarin nucleus is biosynthesized from cinnamic acid through a sequence of ortho-hydroxylation, trans-to-cis isomerization of the side-chain double bond, and subsequent lactonization. Because the trans isomer is too stable to undergo cyclization, conversion to the cis configuration is required, a process attributed to the action of an isomerase enzyme **[12]**.

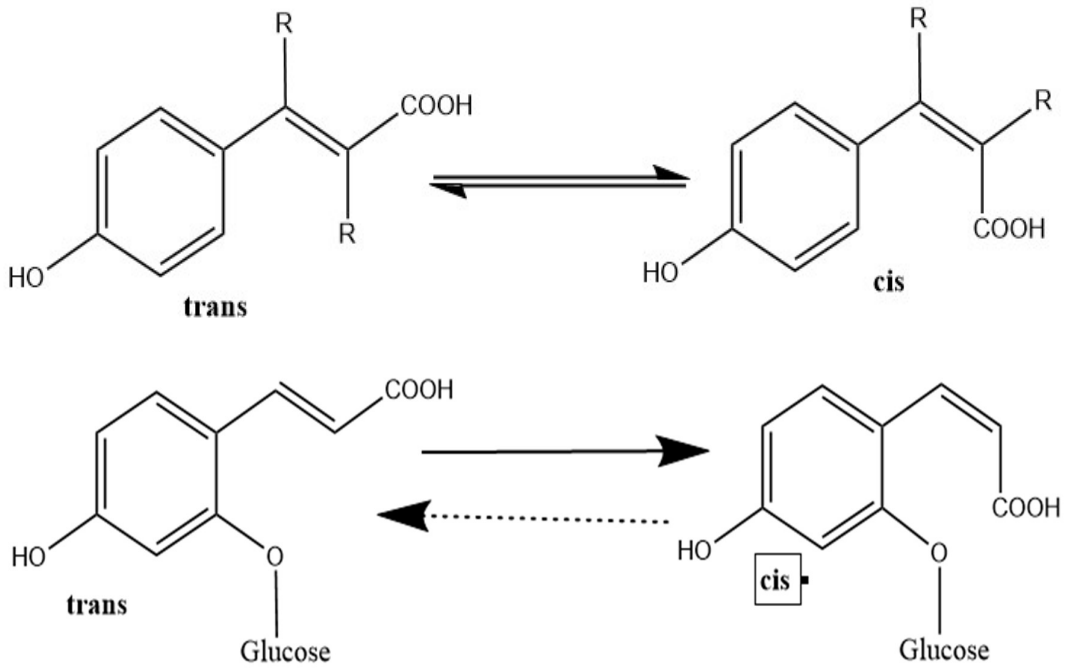
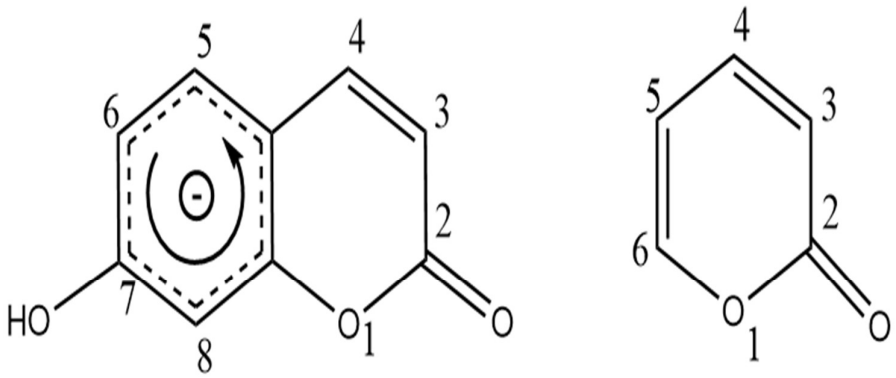


Figure 1.3: Isomerisation of coumarin

The cis isomer is inherently unstable and therefore readily reverts to the more stable trans configuration. During biosynthesis, glucose acts as a leaving group that facilitates this cis–trans interconversion. In *Melilotus alba* (Leguminosae), a β-glucosidase specifically hydrolyzes the cis-glucoside intermediate, enabling progression of the pathway **[12]**. Umbelliferone, esculetin, and scopoletin represent the most widely distributed natural coumarins. This biosynthetic route also explains why naturally occurring coumarins typically bear an oxygen substituent at the 7-position.



7-hydroxy-2*H*-chromen-2-one

2H- 1- benzopyran- 2- one

2*H*-pyran-2-one

Figure 1.4: Isoforms of coumarins and scaffold derivatives

PHARMACOLOGICAL PROFILE

General details

The use of coumarin in clinical medicine was suggested because of its biochemical characteristics. They ought to be assessed for the management of different medical disorders. Interstitial fluid in human tissues drains through the lymphatic system, which is in charge of high-protein edema (HPE). Edema hinders oxygen transmission and tampers with tissue cell metabolism, which makes wound healing difficult. High protein edemas (HPO) are caused by a buildup of protein in the tissue after inflammation or damage, which causes the capillaries to become permeable and allow water to seep into the tissue **[13]**.

High-protein edemas are linked to a variety of illness conditions, from more common and acute forms (like burns and unintentional and surgical traumas) to more severe and chronic forms (like lymphedema and elephantiasis). Several benzopyrones, including coumarin, have been studied for their ability to reduce swelling in high-protein oedema. However, Loprinzi and associates claim that coumarin therapy by itself is ineffective for women who experience arm lymphedema following breast cancer treatment. By incorporating coumarin with other substances into primary combination treatments, it would be feasible to enhance the positive therapeutic effect of coumarin **[14]**.

A recent investigation evaluated the edema-protective efficacy of compression stockings and the vasoactive combination coumarin/troxerutin (SB-LOT) in patients with chronic venous insufficiency after initial leg decongestion, in alignment with current clinical guidelines. The findings support SB-LOT as a viable therapeutic option for patients who are unable to continue compression therapy for extended periods and confirm its effectiveness in preventing recurrent edema in chronic venous insufficiency **[14]**.

ANTICOAGULANT COMPOUNDS

Thrombotic disorders remain a major contributor to morbidity and mortality, driving continuous efforts to identify and develop effective anticoagulant agents. Conventional coumarin-based drugs—such as warfarin, acenocoumarol, cyclocumarol, and dicoumarol—are widely used to limit thrombus propagation and manage conditions including intravascular embolism, thrombosis, and stroke. Despite their clinical utility, these agents exhibit a narrow therapeutic index, leaving patients vulnerable to both insufficient and excessive anticoagulation **[1, 6, 15,16]**.

To overcome these limitations, structurally novel coumarin derivatives are under investigation. Acetamido-substituted coumarin 4a functions as an efficient substrate for platelet calreticulin transacetylase, whereas its acetoxy-

substituted analog 4b demonstrates strong antiplatelet activity by inhibiting platelet aggregation. Carboxyethyl coumarin 5 has shown marked anticoagulant potency accompanied by an extended prothrombin time. Additionally, pyrazole-modified coumarins have emerged as candidates with notable antithrombotic effects.

Activated factor XII (FXIIa) has recently gained attention as a promising molecular target for next-generation anticoagulants **[6]**, primarily due to its potential to separate anticoagulant efficacy from bleeding risk. Halogenated coumarins 7a and 7b have displayed potent FXIIa inhibition, with IC_{50} values of 4.30 and 4.40 μM, respectively. Coumarin derivative 8 also demonstrates anticoagulant activity, although its use is associated with a marked increase in bleeding time.

Given reports of hemorrhagic complications associated with coumarin therapy, recent research has intensified toward elucidating the detailed pharmacologic and toxicologic profiles of coumarin-based anticoagulants to guide the development of safer therapeutic alternatives **[16]**.

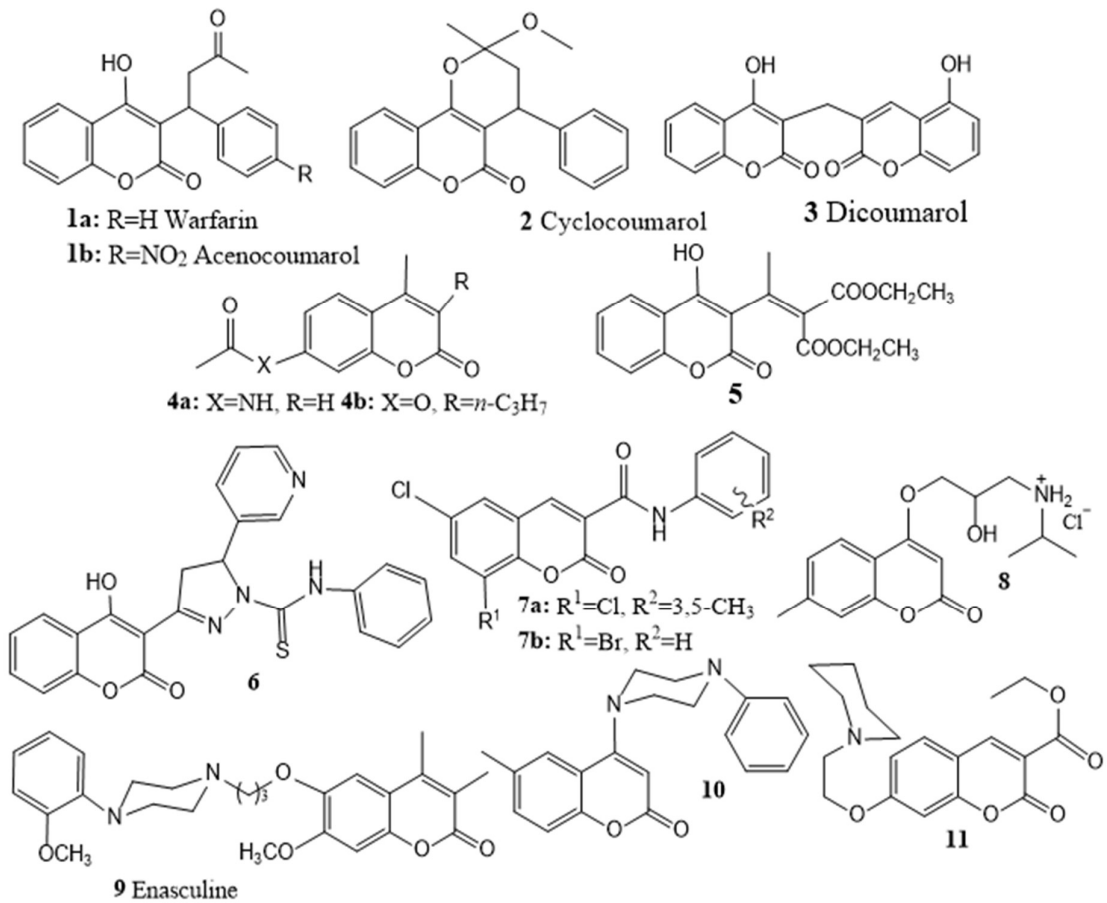


Figure 1.5: Anticoagulant derivatives of coumarins (1-11)

ANTINEURODEGENERATIVE COMPOUNDS

Neurodegeneration, a class of chronic and progressive nervous system diseases, including Alzheimer's and Parkinson's, affects the elderly and significantly impacts their quality of life. Coumarin compounds are effective in treating these diseases **[17]**.

Coumarin Compounds as Medicinal Agents for Anti-Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition that represents a leading cause of dementia in the elderly. Its growing prevalence has created a substantial medical and social burden, driven by pathologic processes such as chronic inflammation, protein misfolding, amyloid-β (Aβ) deposition, oxidative damage, and impaired cholinergic neurotransmission within the basal forebrain. For decades, researchers have sought chemical agents capable of modifying or slowing the course of AD.

Acetylcholinesterase (AChE)—a key enzyme in both the peripheral and central nervous systems—terminates cholinergic transmission by hydrolyzing acetylcholine at synapses and neuromuscular junctions. Inhibition of AChE therefore remains a central therapeutic strategy. Several coumarin-based and structurally related compounds have exhibited promising AChE inhibitory activity, including Ensaculin 9, piperidyl-substituted coumarin 11, quaternary ammonium salts 12a and 12b, analog 13, tetrazole-functionalized coumarin 14, BACE1-targeting butyrylcholinesterase inhibitors, coumarin derivative AP2243 (17), FAAH inhibitors, and coumarin 19, which demonstrated notable dual AChE and BChE inhibition.

Amyloid-β aggregation is believed to be a primary driver of neuronal injury and loss in AD. Blocking or reducing Aβ aggregation has therefore emerged as an alternative disease-modifying strategy. Among the investigated compounds, tetrazole-functionalized coumarin 14 produced a marked reduction in the equilibrium plateau of Aβ aggregation assays, indicating strong potential as an anti-amyloid agent.

Overall, while the discovery of effective AChE inhibitors continues to be a central focus of AD drug development, current research trends emphasize the design of bis-target or multitarget-directed ligands capable of simultaneously modulating cholinergic activity, Aβ aggregation, oxidative stress, and other interconnected pathological pathways **[17-20]**.

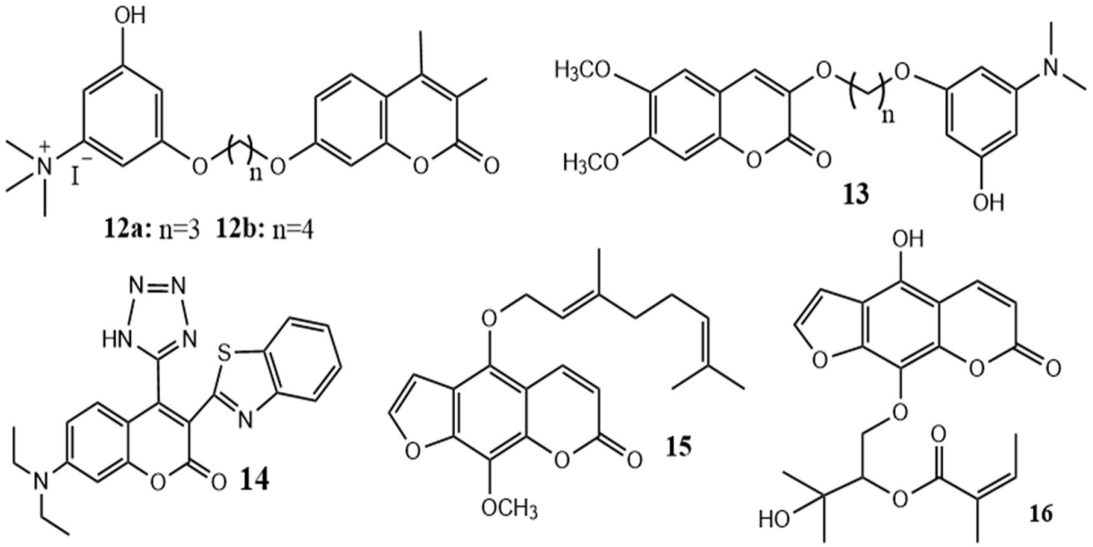


Figure 2: Anti-Alzheimer Coumarin derivatives (12-16)

Coumarin Compounds as Medicinal Agents for Anti-Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder predominantly affecting older adults and characterized by bradykinesia, rigidity, and resting tremor. Monoamine oxidase (MAO) inhibitors remain an important therapeutic class for PD management **[21]**. MAO is a flavin-dependent enzyme that catalyzes the oxidative deamination of endogenous monoamine neurotransmitters, trace amines, and various amine-containing xenobiotics. The two isoforms, MAO-A and MAO-B, are encoded by separate genes and exhibit distinct tissue distributions. Selective inhibition of MAO-B has produced significant clinical benefits in PD therapy.

Recent studies have identified several coumarin-based compounds as promising MAO-B inhibitors. Coumarin–resveratrol hybrids 20a–c demonstrated strong selectivity toward MAO-B, with derivatives 20a and 20b—both containing two methoxy groups—showing particularly potent inhibitory activity. Hydrazide-substituted coumarin 22a and the methanesulfonyl analogue 22b also displayed notable MAO-B inhibition. Compound 23, featuring an indole moiety at the C-3 position of the coumarin scaffold, exhibited a substantial enhancement in activity, achieving nearly a 50-fold increase. Compound 24 emerged as a highly potent and selective MAO-B inhibitor, distinguished by rapid blood–brain barrier penetration, reversible short-acting inhibition, minimal CYP450 interactions, and low in vitro toxicity **[18]**. Additionally, fused coumarin derivative 25, characterized by an extended conjugated system, showed superior MAO-B inhibitory activity and selectivity compared with the R-(–)-diphenyl reference drug. Collectively, these compounds represent promising leads

for further development as next-generation selective MAO-B inhibitors **[21-24].**

ANTICANCER COMPOUNDS

Cancer poses a significant threat to human health, causing significant mortality rates. Despite the development of various clinical drugs, most have poor curative effects, high toxicity, low selectivity, and severe drug resistance. Developing novel anticancer drugs, such as coumarin compounds, is an emerging mission **[22]**.

Coumarin Compounds as Anticancer Agents Against Breast Carcinoma

Breast cancer remains one of the most prevalent malignancies among women and is frequently driven by estrogen-dependent signaling. Early investigations identified the first coumarin-based steroid sulphatase inhibitor, 667-coumate (26), as a potential therapeutic candidate for estrogen-dependent breast cancer **[25]**. More recent studies have shown that coumarin derivatives can form coumarin–estrogen conjugates and selectively modulate estrogen receptors, further expanding their relevance in breast cancer therapeutics. The recognition of novobiocin's antitumor properties has also renewed interest in coumarins as anticancer scaffolds **[26, 27]**.

Mammea-type coumarins—an extensive group of isoprenylated 5,7-dihydroxycoumarins produced by species of *Mammea*, *Mesua*, and *Calophyllum*—demonstrate diverse biological effects. Among these, compound 27 has been shown to inhibit both hypoxia-induced and iron-chelator–induced activation of hypoxia-inducible factor-1 (HIF-1) in T47D breast tumor cells and to suppress migration of MDA-MB-231 cells.

Heat shock protein 90 (Hsp90) is a validated anticancer target, and several coumarins have been developed as Hsp90 inhibitors. Coumarin 28a exhibits strong potency by inducing proteasome-mediated degradation of multiple Hsp90 client proteins and shows pronounced antiproliferative activity in MCF-7 breast cancer cells. Its derivative, 28b, demonstrates even greater inhibitory efficacy. KU-398 has emerged as a promising lead compound that inhibits Hsp90 activity and displays notable anticancer potential.

Structural modification has also yielded candidates with enhanced activity. A benzothiophene-containing coumarin derivative, 29a—featuring C-3 substitution and removal of the 8-methyl group—exhibited lead-like activity against SKBr-3 and MCF-7 cell lines. Glycosylated coumarin 29b showed excellent inhibition of carbonic anhydrase IX (CA IX) in vitro, with strong selectivity toward tumor-associated CA isoforms **[28]**.

Given the role of aromatase (AR) and steroid-modifying enzymes in estrogen biosynthesis, these pathways also represent important targets in breast cancer therapy.

Compound 31 was identified as a reversible, competitive inhibitor of 17β-hydroxysteroid dehydrogenase type 1, showing a Ki value of 53 nM. Thiophene-incorporated coumarin 32 displayed notable antiproliferative activity against MCF-7 cells. Additionally, neo-tanshinlactone and the pyranocoumarin derivative 36 demonstrated significant growth-inhibitory effects in MCF-7 breast carcinoma models **[29]**.

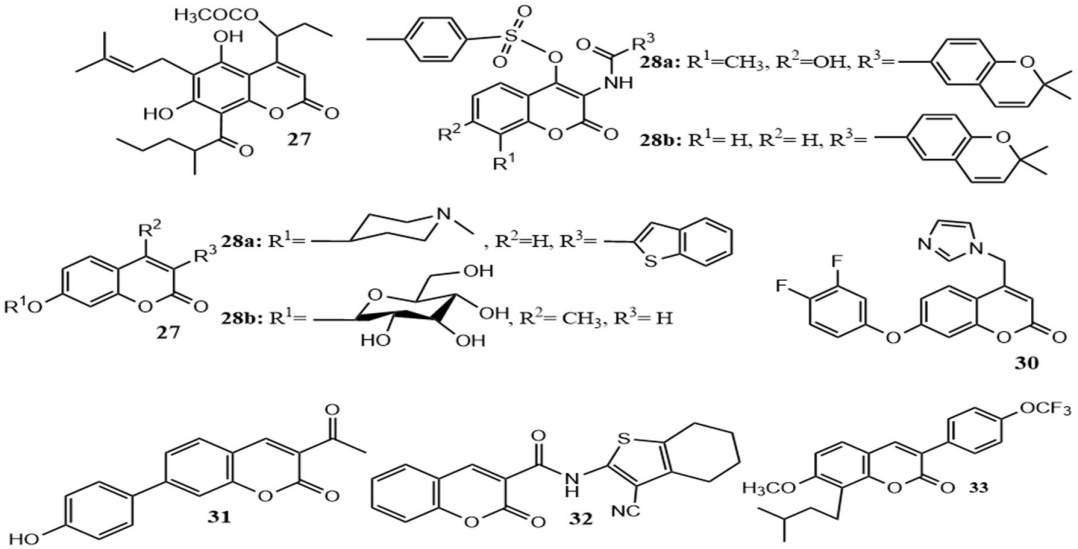


Figure 3: Derivatives for breast carcinoma (26-33)

Coumarin Compounds as Anticancer Agents Against Leukemia

Anaemia, bleeding, infection, and organ invasion are some of the signs of leukemia, a progressive malignant disease marked by aberrant hematopoietic stem cell multiplication. It is a frequent malignant tumor that is very resistant to chemotherapy in children and young people. Recent studies have demonstrated the significance of looking into different chemotherapeutic approaches for the treatment of leukemia. When applied to HL-60 leukemia cells, natural coumarin 37 with a -methylene--lactone moiety demonstrated strong cytotoxicity, resulting in apoptosis and the loss of the mitochondrial membrane. In K562 and K562/A02 leukemia cells, coumarin 38 from *Cicuta virosa* L. exhibited superior cytotoxicity compared to doxorubicin. *Ferula gumosa* having sesquiterpene coumarin 39 had an IC50 value of 8 μM against the leukemia cell lines U-937. Hydroxyphenyl coumarin hybrid 41 showed high potency against HL-60, 7 times more active than resveratrol. Compound 42 showed high antiproliferative activity against U-937 cells, inhibiting their growth at 72 hours **[25, 30]**.

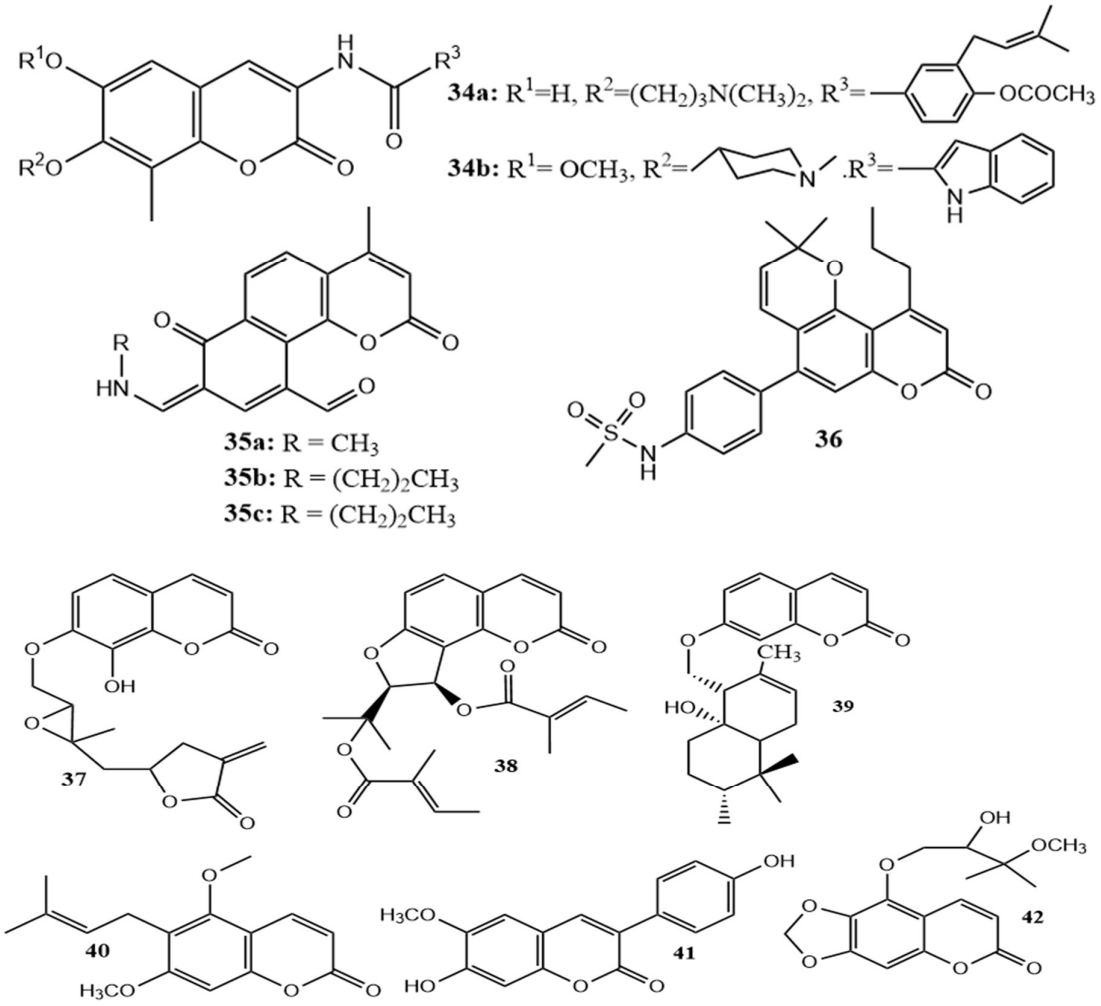


Figure 4: Anti-Leukemic Coumarin derivatives (34-42)

Coumarin Compounds as Anticancer Agents Against Lung Cancer

Lung cancer is a common disease in elderly patients, with only 5% of patients surviving more than 3 years after chemotherapy. This high mortality necessitates the development of improved therapeutic approaches. Resveratrol, a natural polyphenol, has multiple biological activities. Hybrids 43a and 43b, containing resveratrol, showed antiproliferative activity against H-460 lung cancer cell lines. Heterocycles and peptidomimetics containing N-N bonds have been used as pharmaceutical and agricultural agents. Coumarin-based hydrazide-hydrazone 45 showed promising inhibitory effects against non-small cell lung cancer (NCI-H460), and sulfur-bridged coumarin 46 exhibited good antiproliferative activity against A549 lung cancer cell lines. However, replacing the 4-methylcoumarin skeleton with isomeric 2-ethyl-4h-chromen-4-one resulted in a dramatic decrease in activity **[28, 31]**.

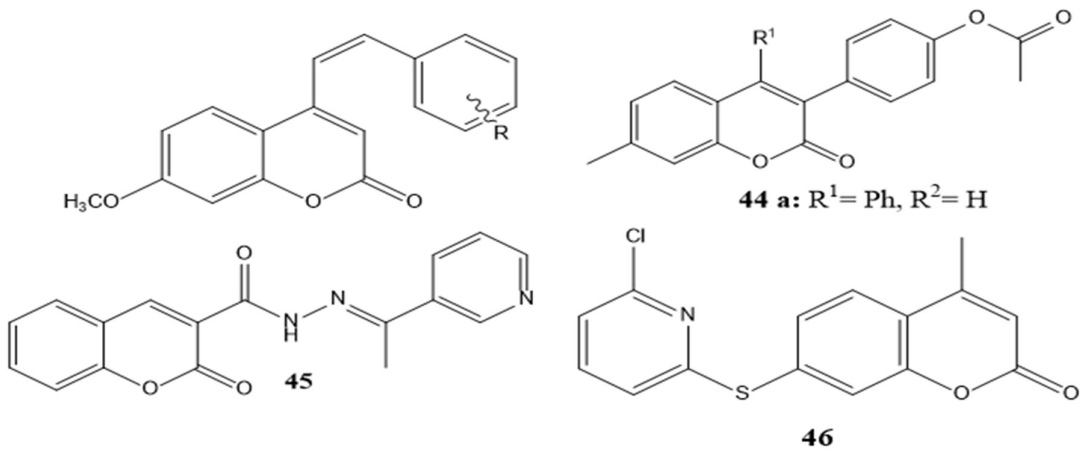


Figure 5: Anti lung cancer coumarin derivatives (44-46)

Coumarin Compounds as Anticancer Agents Against Cervical Cancer

Cervical cancer, a disease-causing bowel and bladder dysfunction, fistula, pain, and bleeding, is primarily caused by high-risk human papillomavirus infection. Despite a 70% drop in mortality rates since 1979, the disease remains prevalent. Fruits can be used as an alternative treatment. Wampee, a fruit, has been found to inhibit the growth of cervical carcinoma cell lines with IC50 values of 0.01 μg/ml. Chalcones, a class of natural products, have shown potential in treating cancer. Chalcone-coumarin hybrids have shown potent anticancer activity, while furocoumarin derivatives have shown potential in photochemotherapeutic drugs. These findings highlight the importance of exploring fruit-based treatments for cervical cancer and other cancers **[32, 33]**.

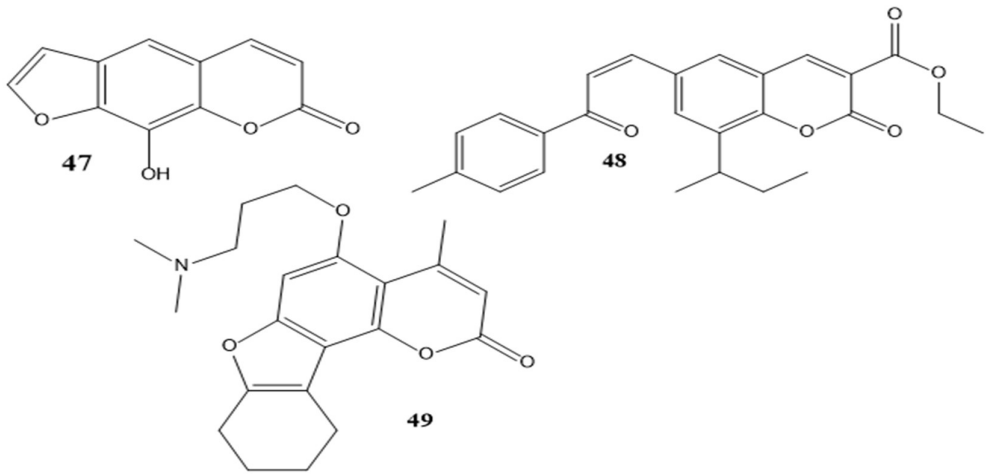


Figure 6: Chalcone-coumarin derivatives for cervical cancer (47-49)

Coumarin Compounds as Anticancer Agents Against Colon Cancer

Colon cancer is a common malignancy, with approximately one million new cases reported worldwide each year. Even after

surgical removal of tumors, nearly 40% of patients experience disease recurrence. To address this, adjuvant therapies, including chemotherapeutic agents, have been explored to lower relapse rates. Citrus fruits are rich in bioactive compounds with potential anticancer properties. For example, natural coumarin 50, extracted from citrus peels, exhibits antiproliferative effects against human colon cancer cells **[34]**. Additionally, novobiocin-derived 2-indoleamide 51 has shown strong inhibitory activity against HCT-116 colon cancer cell lines. Bis-coumarin polysulfides, such as compound 52, have also demonstrated the ability to decrease cell viability and trigger cell cycle arrest **[27, 34]**.

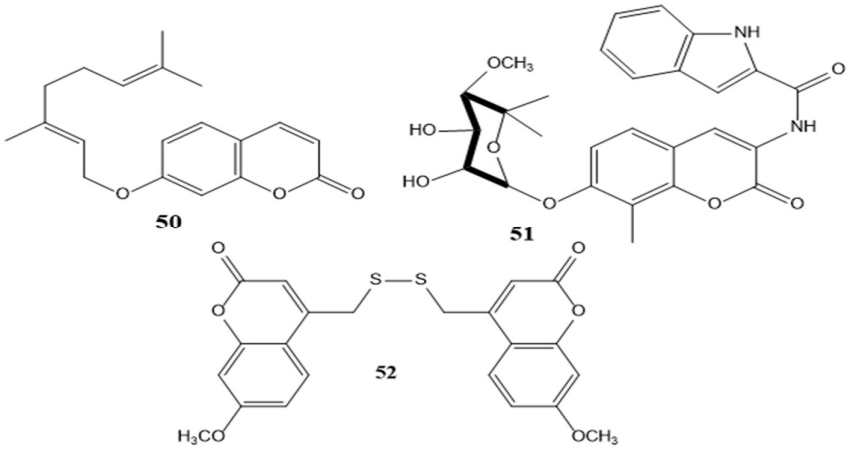


Figure 7: Colonic cancer curing Coumarin derivatives (50-52)

Coumarin Compounds as Anticancer Agents Against Pancreatic Cancer

Pancreatic cancer remains one of the most aggressive malignancies, with a median survival of less than six months and a 5-year survival rate of only around 5.5%. Surgical resection is possible in just 15–20% of patients, and only a minority survive up to five years post-surgery. The tumor's inherent resistance to standard anticancer therapies contributes to frequent treatment failures. *Kayea assamica*, an evergreen tree traditionally used to reduce excessive heat, has shown promising anticancer potential. Extracts from its flowers exhibited complete selective cytotoxicity against human pancreatic PANC-1 cells under nutrient-deprived conditions. Natural coumarin 53 and long-chain isoprenyloxy-modified coumarin 54 demonstrated strong cytotoxic effects against PANC-1 cells **[35]**. Additionally, derivative 55 effectively inhibited human NAD(P)H quinone oxidoreductase-1 (NQO1), an enzyme associated with various tumor types **[36,37]**.

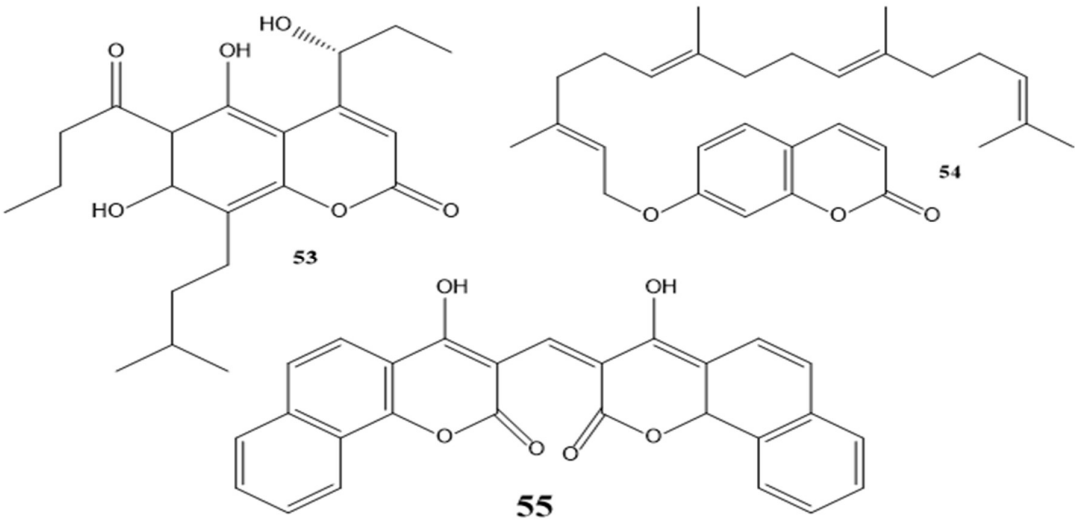


Figure 8: Adenocarcinoma treating drug based on coumarin derivatives (53-55)

Coumarin Compounds as Anticancer Agents Against Gastric Carcinoma

Gastric cancer continues to pose significant treatment challenges, despite a gradual decline in its incidence and mortality. Surgical resection remains the mainstay of therapy, offering only about 30% five-year survival. Palliative chemotherapy can improve both quality of life and overall survival in affected patients. Natural product 56, isolated from *Corydalis heterocarpa*, exhibits strong antiproliferative effects against AGS human gastric cancer cells, reducing cell proliferation by approximately 54%. Telomerase, a critical target in cancer therapy, is often reactivated in tumor cells to support uncontrolled growth. Compound 57, containing a 4,5-dihydropyrazole moiety, displayed enhanced activity against SGC-7901 human gastric cancer cells along with potent telomerase inhibition. Additionally, compound 58 is a novel microtubule inhibitor showing antimitotic effects in 5-fluorouracil-resistant human gastric cancer cell lines **[37]**.

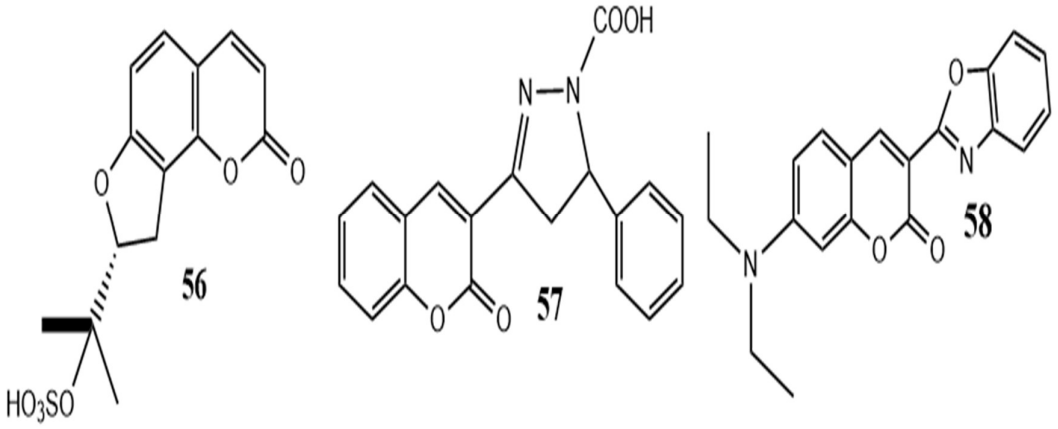


Figure 9: Coumarin derivatives for gastric cancer (56-58)

Coumarin Compounds as Anticancer Agents Against Other Cancers

Coumarin-based compounds have shown promising activity against several malignancies, including mantle cell lymphoma (MCL), prostate cancer, and ovarian cancer. MCL is an aggressive B-cell lymphoma characterized by rapid recurrence, often associated with mutations or overexpression of apoptosis-related genes such as p53, which indicates poor prognosis. Natural coumarin 59, derived from *Calophyllum brasiliense*, demonstrated greater efficacy in MCL cells harboring mutant p53 compared to wild-type p53. In prostate cancer, compound 60, a potential 17-HSD3 inhibitor, exhibited significant therapeutic activity. Ovarian cancer ranks as the eighth leading cause of death among women, with drug resistance driving the development of new treatments. Compound 61, a coumarin-based nifurtimox derivative, inhibits the oncogene ras, downregulates the DNA-PK KU-80 subunit, and activates AKT, leading to apoptosis in platinum-resistant OVCAR-3 ovarian cancer cells. Its in vivo anti-ovarian cancer potential is currently under investigation **[38, 39]**.

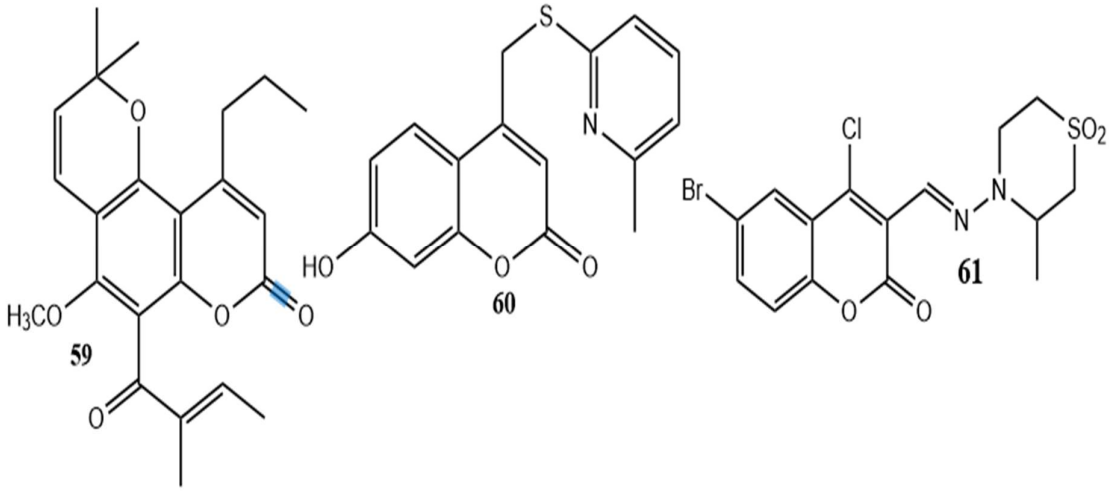


Figure 10: Hydroxysteroid inhibitor derivatives of coumarins (59-61)

ANTIOXIDATIVE COMPOUNDS

Reactive oxygen species (ROS) are natural by-products of aerobic metabolism and play important roles in physiological processes such as signal transduction. However, excessive ROS levels can contribute to aging, neurodegenerative disorders, cardiovascular diseases, inflammation, and cancer. Antioxidant agents can counteract these effects by inhibiting ROS generation, scavenging free radicals, and chelating transition metals. Coumarins demonstrate antioxidant activity, in part, through their ability to bind Fe(III) ions **[36, 40-43]**.

Hydroxyl Coumarins as Antioxidants

Hydroxylated coumarins, particularly 4-hydroxycoumarins, play a crucial role in both the generation and neutralization of reactive oxygen species (ROS), thereby influencing processes mediated by free radicals. Their antioxidant potential is largely attributed to the hydroxyl group, which serves as an effective donor for radical scavenging. Coumarin-based amines have demonstrated notable radical-scavenging activity; for instance, compound 62 exhibits activity comparable to the standard antioxidant BHT. Compounds containing styryl carbonyl moieties, such as 63, also display significant antioxidative effects. Lipoic acid (LA) derivatives 64a and 64b show enhanced hydroxyl radical scavenging activity, outperforming the parent LA. Dihydroxy coumarin derivatives 65a–c have been reported to possess antioxidative properties, with 65b demonstrating the highest DPPH radical scavenging activity. Additionally, benzothiazole-coumarin derivatives like 66 exhibit promising antioxidant activity, achieving notable DPPH scavenging and over 50% ABTS radical inhibition **[44–46]**.

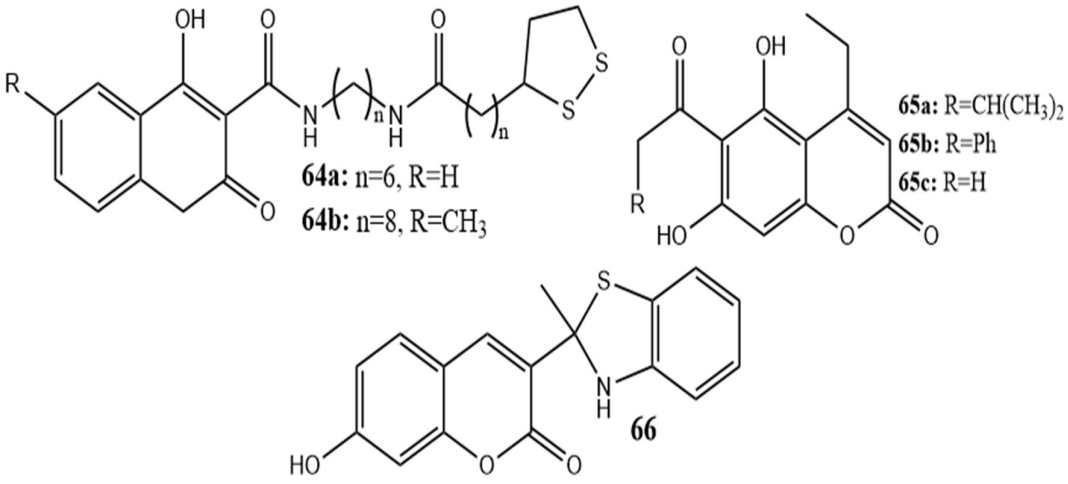


Figure 11: Coumarins hydroxylated antioxidating derivatives (64-66)

Non-hydroxyl Coumarins as Antioxidants

Non-hydroxylated coumarin derivatives also display notable antioxidant properties. For example, 3-3-pyrroline-modified coumarin 67 has been identified as a promising antioxidant agent. Coumarin compounds containing a pyrazolone ring exhibit a broad range of biological activities, with coumarin-based pyrazolone 68 demonstrating moderate DPPH radical scavenging. Oxadiazole-modified coumarin 69 shows comparable antioxidative activity against DPPH and $ABTS^{+}$ radicals. Thiophene and benzothiazole derivatives

are recognized for their analgesic and anti-inflammatory properties. Hybrid compound 70, combining coumarin and benzothiazole, exhibited strong antioxidative activity with 75.64% inhibition relative to ascorbic acid. Similarly, amide-linked coumarin 71 displayed in vitro antioxidant activity comparable to standard ascorbic acid. Coumarin-based Schiff base 72 demonstrated potent radical scavenging, surpassing standards such as BHT, BHA, and ascorbic acid. Lipoxygenases (LOs), a class of iron-containing enzymes, catalyze the oxidation of polyunsaturated fatty acids to lipids. Coumarins 73a and 73b act as effective LO inhibitors, achieving 86% and 62% inhibition, respectively, compared to reference compounds. Further structure-activity relationship studies are ongoing **[37, 47, 48]**.

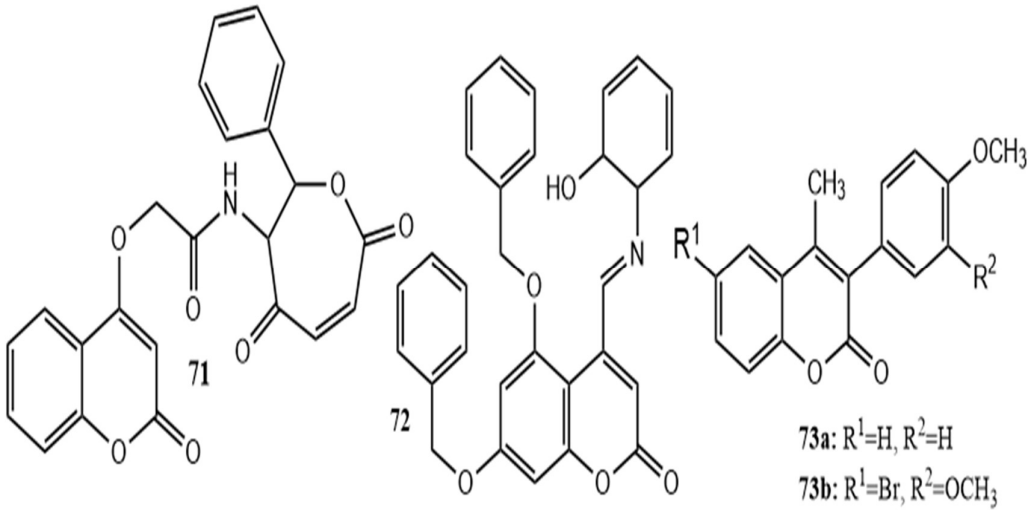


Figure 12: Non-hydroxylated coumarin antioxidant derivatives (71-73)

Fused Coumarin Compounds as Antioxidants

Fused coumarin derivatives, including furocoumarins and pyranocoumarins, have been explored for their antioxidant potential. *Angelica* species, an important medicinal plant, have traditionally been used for their anti-inflammatory, diuretic, and stimulant properties. Natural product 74, isolated from *Angelica urumiensis*, exhibited moderate antioxidant activity. Fused coumarin 75, containing a 1,4-thiazepine moiety, demonstrated notable DPPH radical scavenging activity, while p-chlorophenyl-substituted furocoumarin 76 also showed effective free radical inhibition. Additionally, benzo-coumarin 77 displayed strong lipoxygenase (LO) inhibitory activity, likely due to the presence of a free hydroxyl group **[24, 49]**.

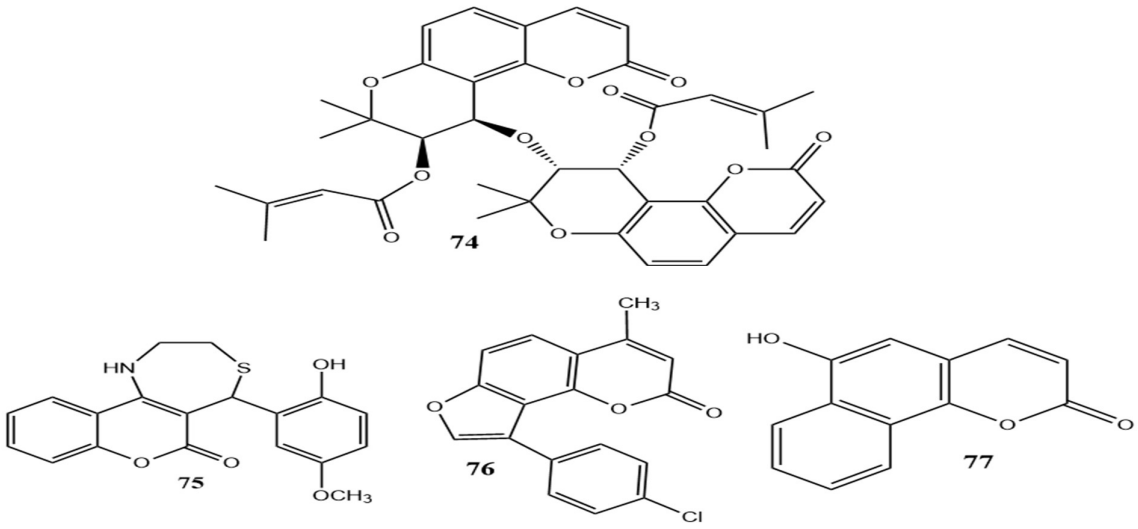


Figure 13: Polycyclic Coumarin antioxidant derivatives (74-77)

CONCLUSION AND OUTLOOKS

Coumarin compounds have been widely explored in medicinal chemistry due to their broad range of biological activities, including anticoagulant, antineurodegenerative, anticancer, antioxidant, antibacterial, antifungal, antiviral, antiparasitic, anti-inflammatory, analgesic, antidiabetic, and antidepressive effects. Among these, significant progress has been achieved in the development of coumarin-based drugs for anticoagulant, antineurodegenerative, antibacterial, anticancer, and antioxidant applications. Future research on coumarins is expected to focus on the discovery, extraction, purification, and identification of naturally occurring coumarins from plants, animals, and microorganisms, as these natural compounds generally exhibit low toxicity and minimal side effects. Structural modification and combination strategies are also being increasingly applied to enhance the biological activity and overcome drug resistance in coumarin-based therapeutics. Additionally, supramolecular coumarin derivatives are emerging as a promising direction, as oxygen-containing conjugated coumarin molecules can form interactions such as hydrogen bonding, ion-dipole, stacking, and hydrophobic forces with other molecular systems. Overall, continued investigation into the chemistry and biological potential of coumarins is expected to contribute significantly to the design and development of new bioactive medicinal agents.

STATEMENT OF ETHICS

There are no animal or human participants used in this study

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AUTHOR CONTRIBUTIONS

Moumita Singha: Conceptualization, literature collection, and manuscript drafting.

Saptarshi Samajdar: Supervision, critical review, and structural organization of the manuscript.

Gourab Biswas: Data curation, graphical illustration, and reference compilation. All authors have read and approved the final version of the manuscript.

ABBREVIATIONS

AD: Alzheimer's Disease; AChE: Acetylcholinesterase; BChE: Butyrylcholinesterase; MAO: Monoamine Oxidase; MAO-B: Monoamine Oxidase type B; PD: Parkinson's Disease; HIF-1: Hypoxia-Inducible Factor 1;ROS: Reactive Oxygen Species; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; LO: Lipoxygenase; FXIIa: Activated Factor XII; NQO1: NAD(P)H Quinone Oxidoreductase-1; CA IX: Carbonic Anhydrase IX; SAR: Structure–Activity Relationship; BHT: Butylated Hydroxytoluene; BHA: Butylated Hydroxyanisole;

CONFLICT OF INTEREST

The authors declare no conflict of interest related to the content or publication of this manuscript. The research was conducted independently without any financial or commercial influence.

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