Applied Chemical Engineering (2025) Volume 8 Issue 4 ISSN: 2578-2010 (O)
doi: 10.59429/ace.v8i4.5813

REVIEW ARTICLE

Coumarins at the interface of chemistry and biology: Applied approaches to synthesis and bioactivity

Yasser Fakri Mustafa*

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, 41001, Iraq

***Corresponding author:** Yasser Fakri Mustafa, Dr.yassermustafa@uomosul.edu.iq

ABSTRACT

Background: Coumarins and their derivatives represent a diverse class of bioactive molecules linking synthetic organic chemistry with modern biomedical applications. Their versatile benzopyran-2-one scaffold allows extensive chemical modification, resulting in derivatives with remarkable pharmacological and photophysical properties. **Aim:** This review aims to summarize advances in the synthesis of coumarin derivatives and to correlate their structural features with biological activities, highlighting their potential as multifunctional agents in applied chemical and biological systems. **Methods:** An integrative analysis of recent literature was performed, encompassing classical and contemporary synthetic strategies—including cyclization, condensation, cross-coupling, and green catalytic methods—and their optimization through computational tools such as molecular docking and quantitative structure–activity relationship modeling. **Results:** The reviewed data reveal that substitution patterns on the coumarin nucleus critically modulate biological activity across a wide range of pharmacological targets. Derivatives exhibit potent anticancer, antimicrobial, antiviral, antifungal, neuroprotective, and cardioprotective effects. Light-responsive and fluorescent coumarins also serve as effective photosensitizers, bioimaging probes, and targeted drug-delivery systems. Environmentally friendly synthetic methodologies and mechanistic modeling further expand the practical applications of these molecules. **Conclusion:** The integration of synthetic innovation, biological evaluation, and computational prediction underscores coumarins as privileged scaffolds at the interface of chemistry and biology. Continued interdisciplinary research is expected to drive the rational design of safer, more selective coumarin-based therapeutics and functional materials for future biomedical and technological applications.

Keywords: coumarin derivatives; synthetic methodologies; biological activity; green chemistry; molecular docking; bioimaging

ARTICLE INFO

Received: 31 October2025
Accepted: 12 November 2025
Available online: 26 November 2025

1. Introduction

The integration of chemistry and biology is anchored in shared molecular architectures that govern vital biological functions[1]. Investigating the design, synthesis, and functional assessment of bioactive molecules enables more precise predictions of their biological behavior. Among these, coumarin and its structural analogues represent an exceptionally versatile class of compounds, participating in diverse biochemical processes[2]. Advances in polymer-based scaffolds and molecular probes have demonstrated that the distinctive photophysical and structural attributes of coumarin derivatives can be effectively exploited for site-specific targeting[3]. Understanding how these derivatives interact with biological receptors enriches the synthesis–activity relationship framework, thereby guiding the rational design of next-generation coumarin analogues

with optimized efficacy[4]. Collectively, these interdisciplinary insights establish fertile ground for innovation at the interface of medicinal chemistry and chemical biology[5].

The contemporary research landscape surrounding coumarins and coumarin-like systems encompasses bioassay-guided design, synthetic development, and molecular dynamics-based activity studies[6]. Coumarins continue to serve as cornerstone structures in the exploration of structure–activity relationships (SAR) characteristics aimed at translational biomedical applications. Their well-documented antioxidant[7], anticancer[8], antiviral[9], antifungal[10], cardioprotective[11], anti-obesity[12], psychoactive[13], and neuroprotective[14] effects sustain widespread scientific interest. More recently, nanostructured carriers, polymeric probes, and coumarin-functionalized materials have been engineered for targeted drug delivery and fluorescence-based bioimaging[15]. Within this expanding synthesis–bioactivity continuum, particular emphasis is placed on understanding how substitution patterns influence biological potency and synthetic feasibility, offering a clearer pathway for tailoring coumarin derivatives toward precise therapeutic and diagnostic goals[16].

2. Chemical foundations of coumarins

Although traditionally defined within a rigid structural framework, coumarins actually encompass a broad and versatile class of bioactive molecules whose SARs continue to inspire research into novel synthetic pathways, structural analogs, and pharmacologically relevant derivatives[17]. The discussion of classical coumarins in the context of synthesis and molecular design reflects both their historical importance and their enduring role as privileged scaffolds in modern medicinal chemistry[18]. The benzopyran-2-one nucleus—a defining structural motif—serves as the foundation for diverse substitution patterns that modulate reactivity, pharmacokinetics, and biological potency[19]. These SAR principles are recurrently explored in relation to synthetic strategies, therapeutic applications, and biological profiles throughout this review.

Coumarin and its derivatives, whether naturally occurring or synthetically derived, exhibit a remarkable spectrum of pharmacological effects. Their reported biological activities include anticancer, antifungal, antiviral, cardioprotective, enzyme inhibitory, and photoactive properties, among others[20]. When evaluated as photosensitizers, attention has been directed toward their photostability and the mechanistic pathways underlying their photo-induced behavior[21]. Comprehensive SAR studies have emphasized the influence of substituents on the coumarin ring system in determining biological efficacy, while molecular docking investigations have elucidated potential interactions between coumarin derivatives and key enzymatic targets—collectively reinforcing their significance in drug discovery and biomedical research[22].

Structural features and substitution patterns

The coumarin framework consists of a fused benzene and α,β-unsaturated carbonyl system forming a lactone ring. Structurally, it represents a six-membered aromatic ring linked to a six-membered lactonized ketone, creating a conjugated system with pronounced electronic delocalization[23]. Electrophilic substitution reactions at specific carbon positions often generate additional five- or six-membered rings, many of which correspond to key pharmacophoric domains[24]. However, electron distribution within the coumarin skeleton is not entirely uniform. The conjugation between the carbonyl and the olefinic double bond facilitates electron migration across the molecule, enhancing the reactivity of the aromatic ring[25]. This electronic behavior underlies the diverse biological activities of coumarin derivatives, which are influenced not only by the parent nucleus but also by substituents at the C-4, C-6, and C-7 positions. Substituents capable of forming intramolecular hydrogen bonds can further stabilize the preferred three-dimensional (3D) conformation, thereby reinforcing biological efficacy[26].

Coumarin and its derivatives occur widely in nature and display a broad spectrum of pharmacological properties[27]. Beyond their biomedical relevance, coumarins are recognized for their strong fluorescent characteristics, serving as essential components in dye probes and natural photosensitizers[28]. The substitution pattern on the coumarin ring critically governs its photophysical and biological behavior, dictating both activity and specificity. These compounds may participate directly in photodynamic reactions or facilitate light-induced detoxification processes through their excited-state interactions[29]. Additionally, coumarin-based molecules can function as ligands or enzyme inhibitors, targeting several biological systems such as HIV-1 integrase, acetyl-, butyryl-, and carboxylesterases, as well as cytochrome P450 isoenzymes[30].

Synthetic strategies: Traditional and modern approaches

Two principal synthetic approaches are generally employed for producing coumarins and their derivatives. The first involves classical ring-forming routes from simple phenolic precursors such as salicylic acid, *o*-hydroxyacetophenone, resorcinol, and coumarin itself. The second relies on modern synthetic strategies that utilize salicylaldehydes and readily tunable electrophilic or nucleophilic reagents. These methods emphasize structural flexibility and enable the preparation of a wide range of substituted coumarins suitable for subsequent biological evaluation[31]. In the traditional approach, coumarin scaffolds are typically generated through cyclization reactions involving phenolic compounds and α-substituted acrylates or α-oxocarboxylic acids[32]. The fundamental benzopyran ring system can also arise from ultraviolet-induced transformations of coumarin derivatives or via condensations between β-oxo acids and *o*-hydroxyarylaldehydes[33]. Notably, an uncommon near-concave orientation of oxygen substituents has been harnessed to yield 1-alkylcoumarins, chlorophyll-related intermediates, and potential precursors of red-fluorescent 4-methyl-7-hydroxycoumarin[34]. Furthermore, acetal-type intermediates have been successfully cyclized under both conventional heating and microwave irradiation, highlighting the synthetic efficiency of microwave-assisted coumarin formation[35].

Over the past few decades, numerous innovative and operationally simple methodologies have emerged for the synthesis of coumarins and their analogues. These advances have significantly broadened the scope of coumarin chemistry, facilitating their exploration as antibacterial, anticancer, anti-inflammatory, antiproliferative, anti-HIV, antituberculosis, and chemopreventive agents[36]. In parallel, considerable attention has been directed toward green and sustainable chemistry, promoting the use of environmentally benign solvents, recyclable catalysts, and energy-efficient techniques[37]. This ongoing interest underscores not only the scientific importance of the coumarin nucleus but also the enduring fascination with its aesthetic and functional versatility, including its role in fragrance design and fine chemical synthesis[38].

3. Synthetic methodologies for accessing coumarins

A wide array of synthetic strategies has been developed to convert easily accessible precursors into coumarins bearing diverse substitution patterns, as illustrated in **Figure 1**. Fundamentally, the construction of coumarin scaffolds involves cyclization reactions responsible for forming the lactone ring and carbon–carbon bond-forming steps that introduce or modify peripheral substituents[39].

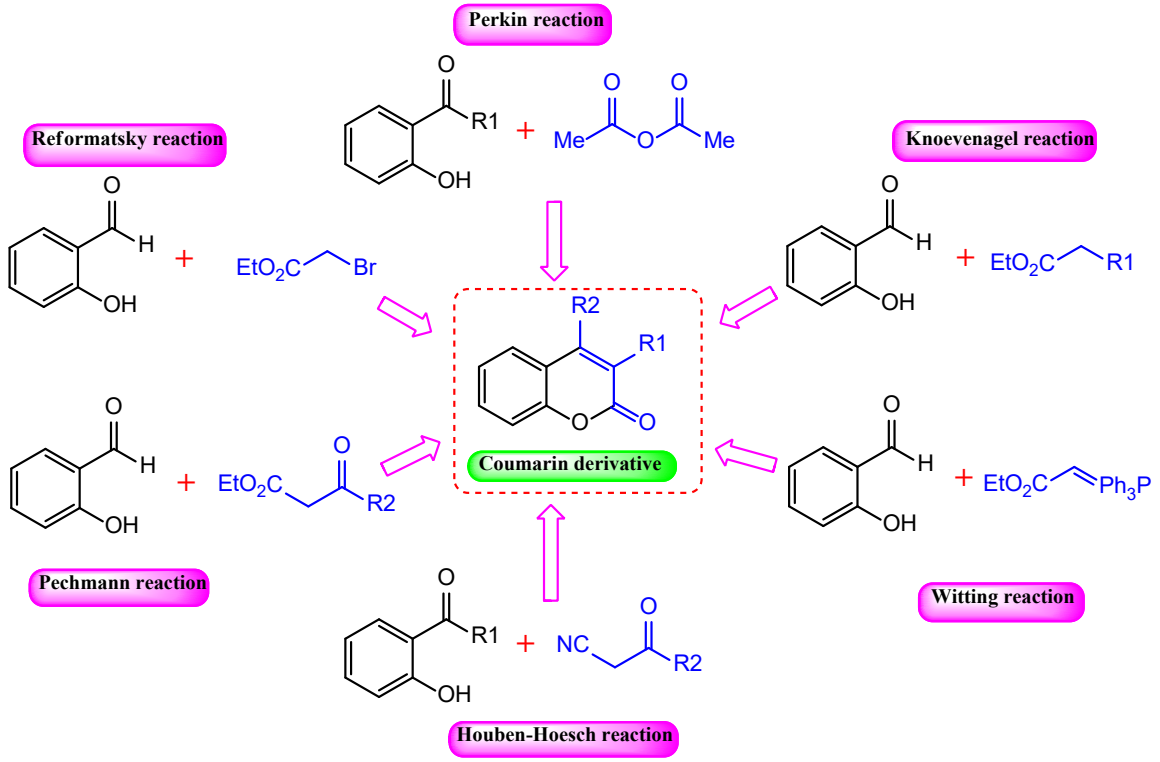

Figure 1. Transforming methodologies for the synthesis of coumarins and their analogues.

Cyclization reactions, which form the characteristic six-membered lactone ring, constitute one of the most straightforward and versatile methods for synthesizing coumarins. These reactions are extensively utilized in both synthetic chemistry and cheminformatics due to their reliability and structural precision[40]. Lactone formation can also be achieved through the acylation of phenolic substrates with keto acids under conditions that preserve the integrity of the core structure or via multi-component synthetic routes. Typically, these coumarin-forming reactions are preceded by steps that introduce alkyl or aryl groups at the C-3 or C-4 positions, ensuring that the subsequent cyclization proceeds from readily available and suitably substituted precursors[41]. Efficient removal of reaction by-products facilitates the formation of poly-substituted coumarins through these cyclization strategies, which can also be adapted for the synthesis of structurally related chromone derivatives[42]. Moreover, selective opening of the coumarin ring provides additional opportunities for functional modification and diversification, enabling the design of a wide range of substituted and tailored derivatives for further investigation[43].

Cyclization and lactone ring formation

Classical cyclization reactions continue to serve as the foundation for the synthesis of coumarins and related analogues. These strategies typically exploit the electrophilic nature of the carbonyl carbon and the pronounced nucleophilicity of the *ortho*- or *para*-position of phenolic substrates, facilitating intramolecular ring closure. In contrast, modern synthetic methodologies have evolved to employ aromatic precursors functionalized with α-ionone-like ketones or keto-esters, enabling the incorporation of diverse coupling partners[44]. This advancement has broadened synthetic access to 3-alkyl- and 3,4-disubstituted coumarin derivatives with improved structural and functional diversity[45]. Catalytic cyclization reactions involving electron-deficient vinyl intermediates have emerged as efficient routes for generating hydroxylated 3-aryl-substituted furanones. Similarly, condensation reactions of *ortho*-oxidized phenolic species—often under metal-catalyzed conditions—remain among the most effective approaches to constructing the coumarin

nucleus[46]. These reactions typically proceed through nucleophilic attack of activated phenolic hydroxyls on electron-deficient α-carbonyl moieties, forming new carbon–carbon bonds in high yields[47].

Modified oxidation-based protocols, such as Swern-type oxidations, have also been adapted to produce 3-halo- and 2,2-dimethyl-substituted coumarins from simple phenolic precursors. The resulting intermediates serve as versatile building blocks for the synthesis of more complex frameworks, including α-diketones, α-tocopheryl glycosides, and γ-branched butyrolactones[48]. Copper-catalyzed coupling reactions have further expanded access to lactone-bearing coumarins and butyrolactone-annulated derivatives through efficient C–C and C–O bond formations[49]. Finally, condensation of silyl-protected phenols with α,β-unsaturated carbonyl compounds provides a thermodynamically favorable pathway to functionalized coumarin–lactone hybrids[50]. These transformations, often related to modified Perkin-type or Schiff-base-assisted reactions, highlight the remarkable versatility of phenolic cyclization chemistry in generating structurally enriched and biologically significant coumarin derivatives[51].

Carbon-carbon bond formations

Carbon–carbon bond formation represents a central step in constructing functionally diverse coumarins. Numerous synthetic methodologies have been developed to extend the π-conjugation of the coumarin nucleus and introduce structural diversity[52]. Among these, transition-metal-catalyzed cross-coupling reactions—including Suzuki, Mizoroki–Heck, Sonogashira, Stille, Negishi, and Buchwald–Hartwig couplings—play a particularly important role. These reactions enable efficient introduction of aryl or alkyl substituents, especially at the C-3 and C-4 positions, thereby enhancing both the electronic and steric versatility of the scaffold[53]. Additionally, thioester-mediated thiol–Yláng transformations have been employed to further expand the synthetic scope toward sulfur-containing analogues[54].

Although less frequently used, annulation strategies have also been explored to generate new coumarin cores and their oxygenated derivatives via cascade or domino processes. For instance, the direct acylation of commercially available monochlorocoumarins with acyl chlorides proceeds smoothly under mild conditions, favoring substitution at the C-6 position due to its intrinsic electronic reactivity[55]. Similarly, nucleophilic addition–dehydration reactions of C-7-dialkyl-substituted coumarins yield silylether intermediates, which can be transformed into chromeno[4,3-*b*]quinone frameworks through one-pot catalytic processes[56].

Microwave-assisted cyclization followed by acid-mediated aromatic nucleophilic chloro-methylation has also been demonstrated as an efficient route to produce naturally occurring 7-benzylated 4-pyrone scaffolds. These pyrone intermediates can be further coupled with 8-formyl-substituted coumarins through one-pot reactions, allowing modular access to complex architectures[57]. More recently, C-6-alkynylated 3-methylcoumarins have been shown to undergo mercuration, enabling subsequent addition of organozinc reagents to afford C-6-alkyl-substituted derivatives in excellent yields[58]. Collectively, these versatile methodologies highlight the growing potential of modular carbon–carbon bond-forming strategies in optimizing the synthesis and functional diversity of coumarin derivatives.

Green and catalytic methods

Environmentally benign catalysts and green solvent systems have demonstrated high efficiency in promoting reactions that yield coumarin-based frameworks. In line with the increasing global emphasis on sustainable methods for organic synthesis, particularly for biologically active and naturally derived compounds, a novel approach was established for coumarin synthesis[59–61]. This method employs carbohydrate-derived dialdehydes as key precursors in the presence of 2,6-dimethylpyridinium 4-sulfonate under microwave irradiation[62]. The microwave-assisted protocol not only enhances reaction rates and yields but also minimizes environmental impact, offering a practical route for generating coumarin derivatives with potential biological significance[63].

Moreover, 1-arylcoumarins bearing free hydroxyl groups or 4-substituted derivatives can be efficiently prepared via one-pot reactions involving 1-(2-hydroxyphenyl)ethan-1-ones and aryloxyl- or arylsulfamoyl-substituted acrylates. The latter intermediates are synthesized through acetylene–sulfonamide coupling, and the overall reaction proceeds smoothly in the presence of catalytic trifluoroacetic acid[64]. In another synthetic strategy, 6-hydroxy-4-methyl-2-phenyl-4*H*-pyran-3,5-dione—functioning dually as a 1,3-dicarbonyl and an α,β-unsaturated carbonyl compound—undergoes a three-component reaction with 2-substituted 3-oxobutanedinitriles and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, affording a new class of 4*H*-pyran-4-ones featuring coumarin fragments[65]. Additionally, the role of quaternary phosphonium salts as probes for assessing the nucleophilicity of azole and thiophene rings has been explored in the synthesis of 4-substituted coumarins[66]. Finally, 3-hydroxy-2-benzothiazolyl-4*H*-chromen-4-one derivatives have been successfully obtained through a simple one-pot transformation of 3-hydroxy-2-benzothiazolyl-4*H*-pyran-4-ones with *ortho*-aminophenols. This transformation is proposed to proceed via sequential cyclocondensation and cyclodehydration steps, offering an efficient route to structurally diverse and biologically promising coumarin analogues[67].

4. Biological activity and mechanistic insights

Biological activity remains the central factor driving scientific and technological interest in coumarins. These compounds exhibit remarkable versatility, engaging multiple molecular targets across diverse biochemical pathways that underpin their therapeutic, pharmacological, and even technological relevance[68]. A comprehensive understanding of the structural and electronic features governing coumarin bioactivity not only bridges the gap between synthesis and application but also provides insights for future developments, particularly in integrating biological efficacy with safety and toxicological assessments[69].

The intrinsic structural framework of coumarins enables selective interactions with key enzymes and receptors, making them valuable scaffolds in medicinal chemistry. Their inherent fluorescence has further expanded their role as probes in bioimaging and sensing technologies[70]. Structural modifications—particularly variations in substituent type and spatial orientation—have proven crucial for modulating enzyme inhibition and biological potency. Consequently, extensive SAR studies have been conducted on both halogenated[71,72] and non-halogenated[73,74] coumarin analogues exhibiting anticancer, antibacterial, antiviral, and antifungal properties. Complementary molecular docking investigations have elucidated binding modes and guided the rational design of more active derivatives[75]. Several coumarin-based compounds demonstrate potent bioactivity with minimal toxicity, and recent efforts have explored their formulation as prodrugs to enhance pharmacokinetic profiles and targeted delivery[76]. Additionally, photoresponsive coumarins have shown promise as photosensitizers in photodynamic therapy and as photoreactive agents capable of regulating controlled drug release, highlighting their dual potential in both therapeutic and material science contexts[77].

Photosensitizers and photobiology

Coumarin-based molecules exhibit remarkable photochemical behavior, particularly their ability to sensitize molecular oxygen and participate in fluid-phase photocycloaddition reactions under light stimulation[78]. Their function as photosensitizers has gained growing attention in photodynamic therapy as well as in chemical and biochemical applications. In this context, the role of the coumarin nucleus as a photosensitizing agent is critically examined, emphasizing the key processes that follow photoexcitation, the fundamental photophysical parameters that determine photosensitizing efficiency, methods for assessing triplet-state quantum yields, and the broader implications of these findings for applied research[79].

Heterocyclic frameworks featuring extended π-conjugation are ideal for photo-induced transformations, as their photophysical properties can be finely tuned by adjusting the number of π-bonds or introducing specific substituents[80]. Among them, coumarin derivatives stand out due to their high fluorescence quantum yields

and moderate triplet-state energies, which together enable efficient singlet oxygen generation[81]. This dual property renders coumarins highly suitable as active oxygen sensitizers while simultaneously allowing dynamic monitoring of photo-induced reactions within coumarin-based systems[82]. In addition, their intense fluorescence and UV-absorbing characteristics have led to the widespread use of coumarins as fluorescent probes and ultraviolet filters, particularly in cosmetic formulations[83]. Recently, several patented products have incorporated coumarins as core active components, including advanced photoprotective sunscreens and optical dyes designed to safeguard sensitive tissues[84]. Consequently, fundamental investigations into the photochemical and photophysical behavior of coumarins are paving the way for innovative applications in medicine, materials science, and photonics.

Enzyme inhibition and pharmacophores

Key enzymatic systems play a pivotal role in mediating the pharmacological effects of coumarins. These compounds modulate a wide spectrum of biological targets, including enzymes such as protein kinases[85], 5-lipoxygenase[86], and topoisomerase II[87]. Among these, the latter is particularly significant, as both natural and synthetic coumarins have demonstrated potent anticancer activity through its inhibition[88]. Other notable enzyme targets sensitive to coumarins include acetylcholinesterase, tyrosinase, bacterial DNA gyrase, lipase, xanthine oxidase, monoamine oxidase, and ribonucleotide reductase[89].

SAR analyses have been instrumental in identifying the molecular determinants that enhance coumarin–enzyme interactions. Functional groups such as hydrogen bond donors and acceptors, hydrophobic domains, and other pharmacophoric features contribute to the affinity and specificity of binding at enzyme active sites[90]. These structural insights are particularly evident in recent coumarin derivatives designed to inhibit cholinesterase, xanthine oxidase, 5-lipoxygenase, and 3-chymotrypsin[91]. For example, quinolinyl-substituted coumarins have been shown to inhibit 5-lipoxygenase, a key enzyme involved in the biosynthesis of proinflammatory leukotrienes associated with asthma and allergic reactions[92]. Computational docking studies reveal that binding within the 5-lipoxygenase catalytic pocket is primarily stabilized by interactions involving the coumarin carbonyl and the nitrogen atom of the quinoline ring[93]. The derived 3D pharmacophore model highlights one hydrogen bond acceptor and one lipophilic site as critical features for activity[94].

Similarly, coumarin-based hybrid inhibitors targeting cholinesterases—enzymes implicated in Alzheimer's disease—have been rationally designed to include a carbamate group as a reversible inhibitory moiety, together with acetyl or carbonyl functionalities that enable Michael-type covalent interactions[95]. Additional linkers or substituents refine the molecular geometry, allowing optimal alignment within the enzyme's active site. SAR evaluations confirm that 3D orientation and spatial arrangement are essential for high potency, a finding further supported by 3D pharmacophore models comprising three key interaction components essential for effective enzyme inhibition[96].

Structure–activity relationships

SAR analyses provide essential understanding of how specific molecular modifications influence biological responses and therapeutic outcomes. By systematically linking structural variations to bioactivity, SAR studies serve as a cornerstone for rational drug design and the prioritization of lead compounds[97]. In the case of coumarins and their derivatives, distinct substituent patterns play a decisive role in determining biological targets and mechanisms across diverse therapeutic areas[98].

Monocyclic coumarins featuring a four-atom lactone core exhibit marked effects on enzymes such as tyrosinase and thymidylate synthase, both of which are key targets in anticancer therapy. Insights into enzyme–ligand interactions involving the coumarin nucleus have facilitated the rational design of more potent 3-substituted analogues with enhanced enzyme affinity[99]. Moreover, variations in substitution patterns significantly modulate inhibitory activity toward tubulin polymerization, a critical pathway in tumor cell

division[100]. The positioning of phenolic and furan moieties also exerts strong control over cytotoxic potential against various cancer cell lines, including those incorporating five-membered beryllium-linked units[101].

A notable example is 7-(3,4-dihydroxy-5-pentenyloxy)benzothiocoumarin, which demonstrates pronounced cytotoxicity against breast cancer (MDA-MB-231), colorectal (HCT-15, HT-29), and lung (TRC-50, NCI-H460, A549) cell lines by interfering with the thymidylate synthase–thymidine kinase complex[102]. Furthermore, selective monofunctionalization of the phenyl ring enhances halogen-binding affinity, effectively targeting methicillin-resistant *Staphylococcus aureus* through inhibition of dihydrofolate reductase[103]. The presence of a hydroxyl substituent is also critical for interactions with adenosine kinase, underscoring how minor structural alterations can profoundly influence binding behavior and biological efficacy[104].

5. Therapeutic and pharmacological applications

A diverse array of coumarins and their structural analogues display remarkable pharmacological properties, as illustrated in **Figure 2**. The biological potential of coumarins is closely linked to the distinctive structural elements of their core nucleus—particularly the carbonyl functionality at the C-2 position. These functional moieties enhance molecular recognition by mediating versatile interactions with biological macromolecules such as proteins, nucleic acids, and lipids[105]. Moreover, the *cis*-pentadienyl side chain, distinguished by its conjugated double-bond system, plays a crucial role in photochemical processes[106]. Acting as a principal chromophore in plant chloroplasts, it readily participates in the formation of reactive oxygen species, including singlet oxygen and triplet excited states. The subsequent interaction of singlet oxygen with coumarin derivatives often leads to the generation of various oxidized products, such as naphthoquinones, carboxylic acids, and aromatic derivatives, further underscoring the structural versatility and reactivity of the coumarin framework[107].

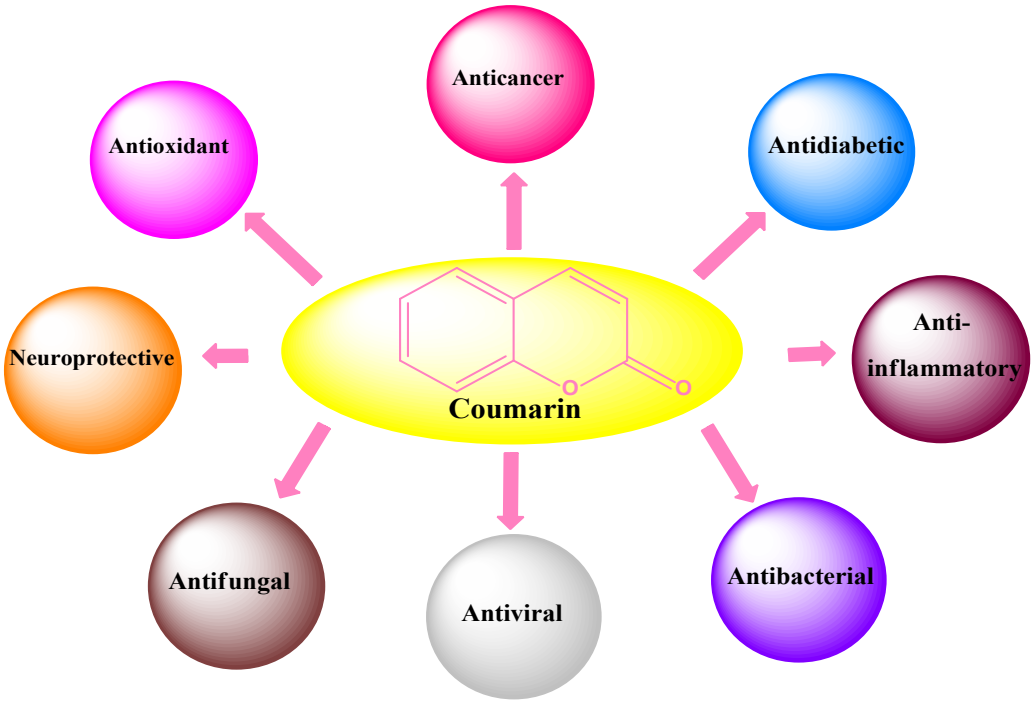

Figure 2. Therapeutic and pharmacological applications of coumarins and their analogues.

Coumarins can also associate with specific proteins through non-covalent interactions, contributing to their photostability and enhancing their role as photosensitizers in photodynamic cancer therapy[108]. Their ability to transfer energy and electrons enables them to react with diverse biological substrates, including nucleic acids, proteins, and membrane lipids, thereby inducing targeted cytotoxic effects in tumor cells. From

a therapeutic standpoint, coumarins represent a versatile scaffold for drug discovery[109], as shown in **Figure 3**. Several derivatives have demonstrated the ability to inhibit multidrug-resistant microbial and viral strains by suppressing overexpressed transport proteins, thereby overcoming resistance mechanisms[110]. Moreover, hydrophilic coumarins such as 7-hydroxy- and 7-methoxy-4-pyridin-3-yl-coumarins exhibit the capacity to penetrate the blood–brain barrier and protect human neuroblastoma SH-SY5Y cells from oxidative-stress-induced neuronal injury[111]. Other coumarin analogues have been identified as selective inhibitors of protein–DNA[112] and protein–protein[113] interactions, as well as modulators of blood coagulation with minimal influence on the fibrinolytic system[114].

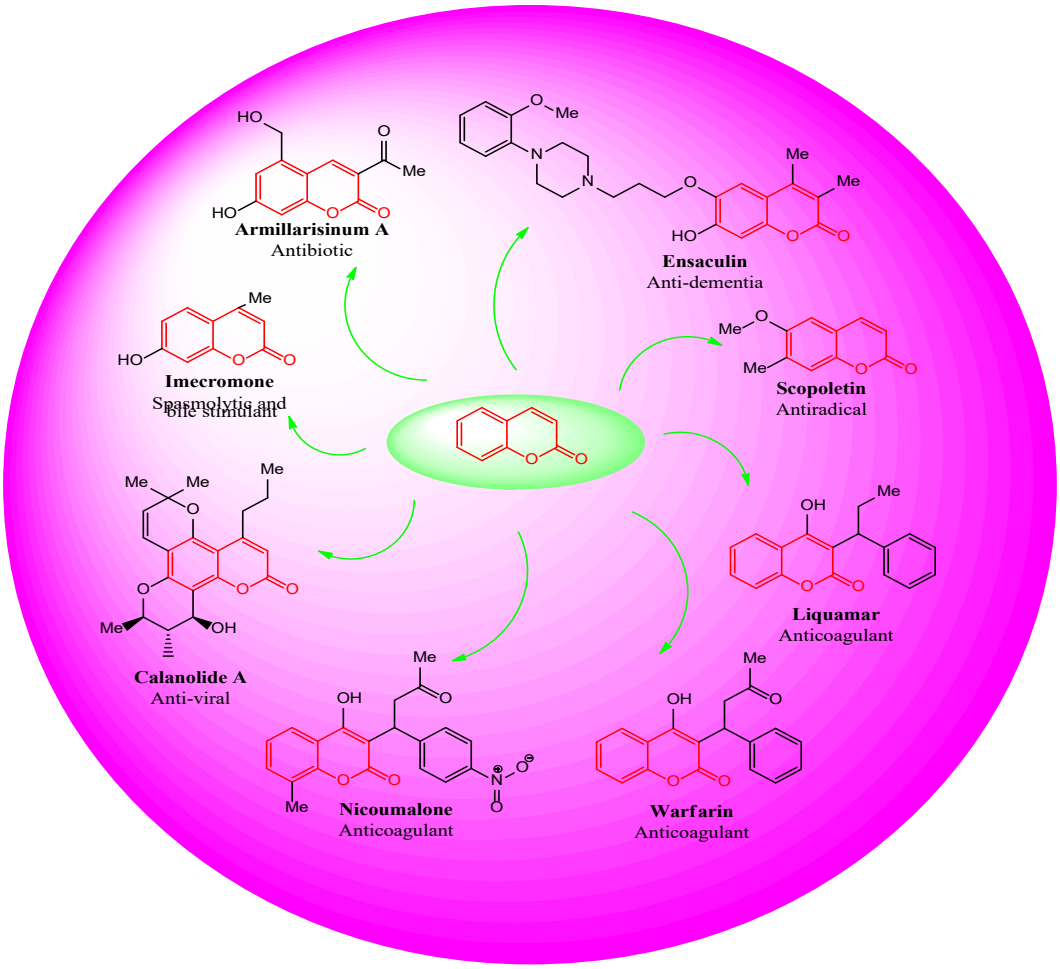

Figure 3. Examples of some coumarins with approved therapeutic effects.

Anticancer and antibacterial activities

Coumarin derivatives have attracted significant attention in anticancer drug discovery owing to their broad spectrum of cytotoxic mechanisms and structural versatility. Their antitumor potential is primarily linked to their ability to interfere with multiple molecular targets involved in cancer cell proliferation, apoptosis, angiogenesis, and metastasis[115]. Many coumarin-based compounds act by inhibiting key enzymes such as topoisomerases, protein kinases, and aromatases, thereby disrupting vital cellular signaling pathways[116]. Substitutions at the 3-, 4-, and 7-positions of the coumarin nucleus often enhance binding affinity to target proteins, improving selectivity and potency[117]. Furthermore, coumarins have demonstrated the ability to induce oxidative stress and mitochondrial dysfunction in cancer cells, leading to the activation of intrinsic apoptotic cascades[118]. Some derivatives, such as warfarin analogues and 7-hydroxycoumarins, also inhibit angiogenesis by suppressing vascular endothelial growth factor expression[119]. Their multitarget nature, low

toxicity, and favorable pharmacokinetic profiles make them promising scaffolds for developing novel chemotherapeutic and chemopreventive agents, particularly when combined with other pharmacophores in hybrid structures[120].

In addition to their anticancer potential, coumarin derivatives exhibit potent antibacterial activity against a wide range of Gram-positive and Gram-negative bacteria. Their antimicrobial efficacy is often associated with the presence of electron-donating[121] or electron-withdrawing[122] substituents that enhance lipophilicity and membrane permeability. Mechanistically, coumarins inhibit bacterial DNA gyrase and topoisomerase IV—enzymes crucial for DNA replication and transcription—resulting in cell cycle arrest and bacterial death[123]. Some coumarin derivatives also interfere with bacterial quorum sensing and biofilm formation, reducing pathogenicity and antibiotic resistance[124]. Natural coumarins such as umbelliferone and scopoletin, as well as synthetic analogues bearing halogen, nitro, or amino groups, have shown pronounced antibacterial effects even against multidrug-resistant strains[125]. The relatively low cytotoxicity of these compounds toward mammalian cells, combined with their broad antimicrobial spectrum, underscores their potential as lead molecules for next-generation antibacterial agents capable of overcoming current resistance challenges[126].

Antiviral and antifungal potential

Coumarin derivatives have attracted considerable scientific attention for their broad-spectrum antiviral properties, which stem from their diverse structural modifications and ability to interfere with key stages of viral replication. Several natural and synthetic coumarins have been reported to inhibit the replication of RNA and DNA viruses, including Zika virus, Dengue virus, human immunodeficiency virus, and herpes simplex virus[127]. The antiviral activity of coumarins is often attributed to their capacity to modulate viral enzymes such as reverse transcriptase, protease, and helicase, or to disrupt host–virus interactions essential for viral propagation[128]. For instance, studies have shown that certain hydroxylated and prenylated coumarins can suppress viral RNA synthesis and reduce viral load in cell-based assays. SAR analyses highlight the importance of substitutions at the 7- and 8-positions of the coumarin ring, which can significantly influence lipophilicity, target binding, and overall antiviral potency[129]. Moreover, molecular docking and 3D quantitative SAR models have been used to design novel anti-Dengue and anti-Zika coumarins, offering a promising pathway for the development of selective and potent antiviral agents[130].

In addition to their antiviral effects, coumarin derivatives have demonstrated substantial antifungal activity against a wide range of pathogenic fungi. Natural coumarins isolated from plants such as *Steganotaenia araliacea* and *Melilotus officinalis* have shown inhibitory effects against *Candida* species, *Trichophyton mentagrophytes*, and *Cryptococcus neoformans*[131]. The antifungal mechanism of these compounds is believed to involve disruption of fungal cell membrane integrity, inhibition of ergosterol biosynthesis, and interference with mitochondrial oxidative processes. Structural modification of the coumarin nucleus, particularly through the introduction of halogen, methoxy, or glycosidic substituents, has been shown to enhance antifungal potency and selectivity[132]. Reduced glycoside-based coumarin derivatives, for example, exhibit strong inhibition of *Candida albicans* and *Candida tropicalis*, alongside moderate activity against *Candida glabrata*[133]. Furthermore, coumarin derivatives have been explored for their synergistic potential when combined with conventional antifungal drugs, leading to improved therapeutic outcomes and reduced resistance[134]. Recent computational and experimental studies also suggest that coumarins may act as inhibitors of matrix metalloproteinases, which could contribute to their antifungal efficacy and broaden their therapeutic scope[135].

Neuroprotective and cardiovascular effects

Coumarin derivatives have attracted considerable attention for their neuroprotective potential, primarily due to their multifunctional mechanisms that address the complex pathophysiology of neurodegenerative

disorders such as Alzheimer's (**Figure 4**), Parkinson's (**Figure 5**), and Huntington's (**Figure 6**) diseases. Their antioxidant, anti-inflammatory, and metal-chelating properties make them capable of mitigating oxidative stress and neuronal damage—two major hallmarks of neurodegeneration[136]. Several coumarin analogues have demonstrated the ability to inhibit acetylcholinesterase and butyrylcholinesterase, thereby enhancing cholinergic neurotransmission and improving cognitive performance[137]. Moreover, these compounds have shown the capacity to suppress neuroinflammatory mediators such as TNF-α and IL-6 through modulation of NF-κB and MAPK signaling pathways. In addition, certain substituted coumarins can chelate excess metal ions like Fe^{+2} and Cu^{+2}, preventing metal-induced aggregation of amyloid-β peptides and neuronal apoptosis[138]. The neuroprotective efficacy of hybrid coumarins containing pharmacophores such as carbazole, indole, or triazole has also been reported, suggesting that rational structural modification can amplify their multi-target neurotherapeutic potential[139].

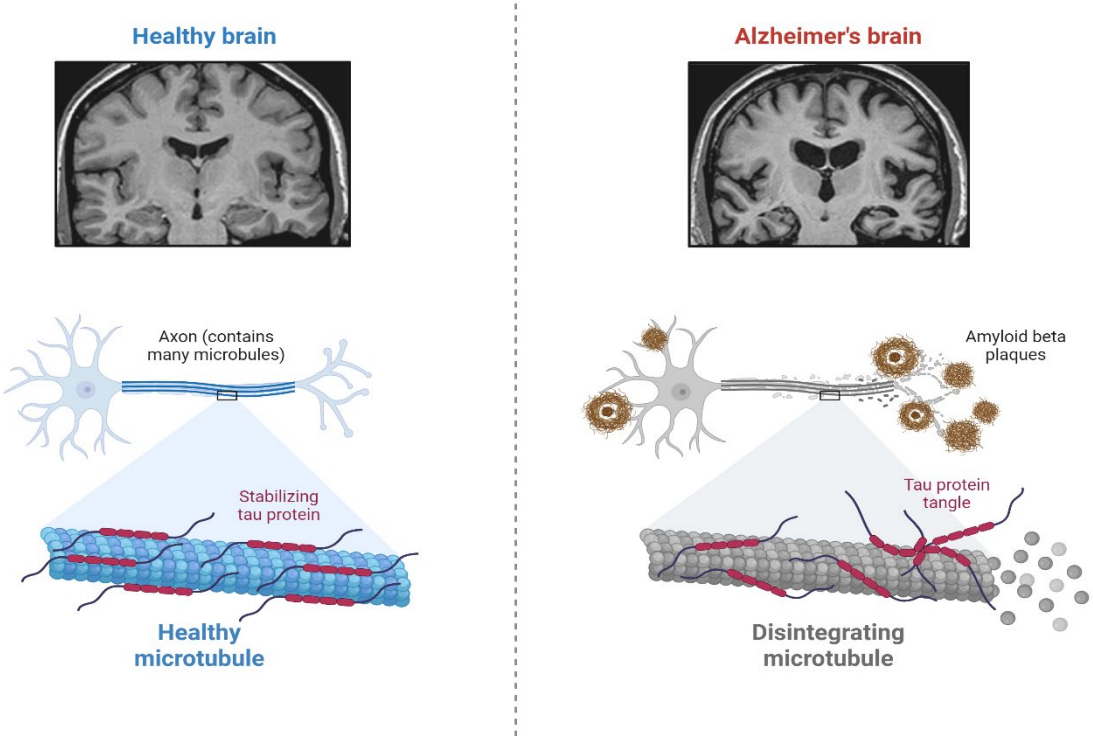

Figure 4. Pathology of Alzheimer's disease.

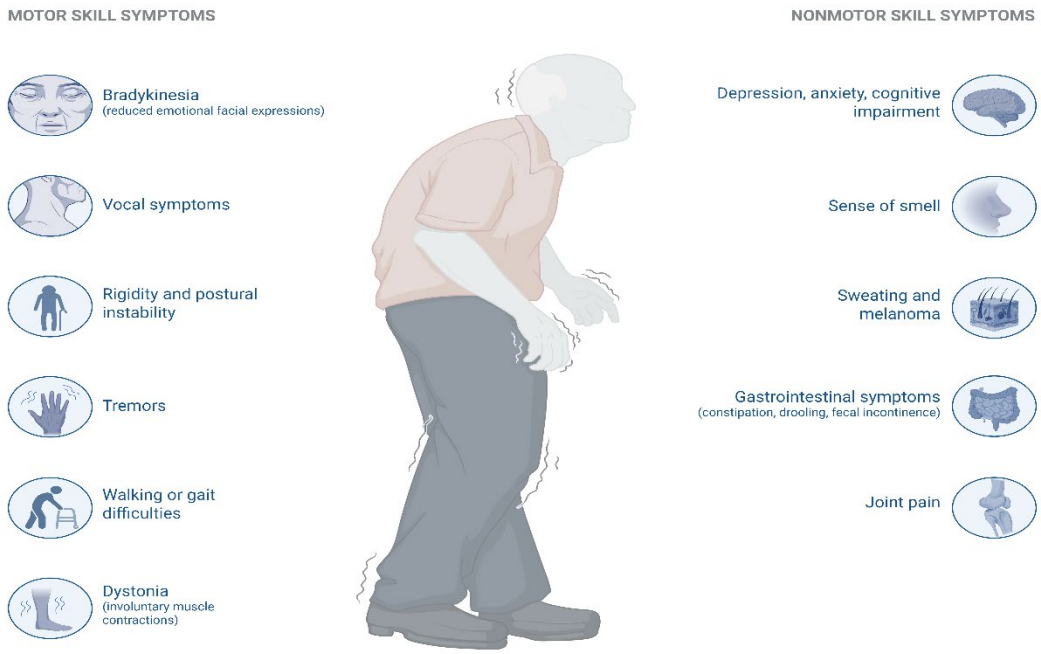

Figure 5. Symptoms of Parkinson's disease.

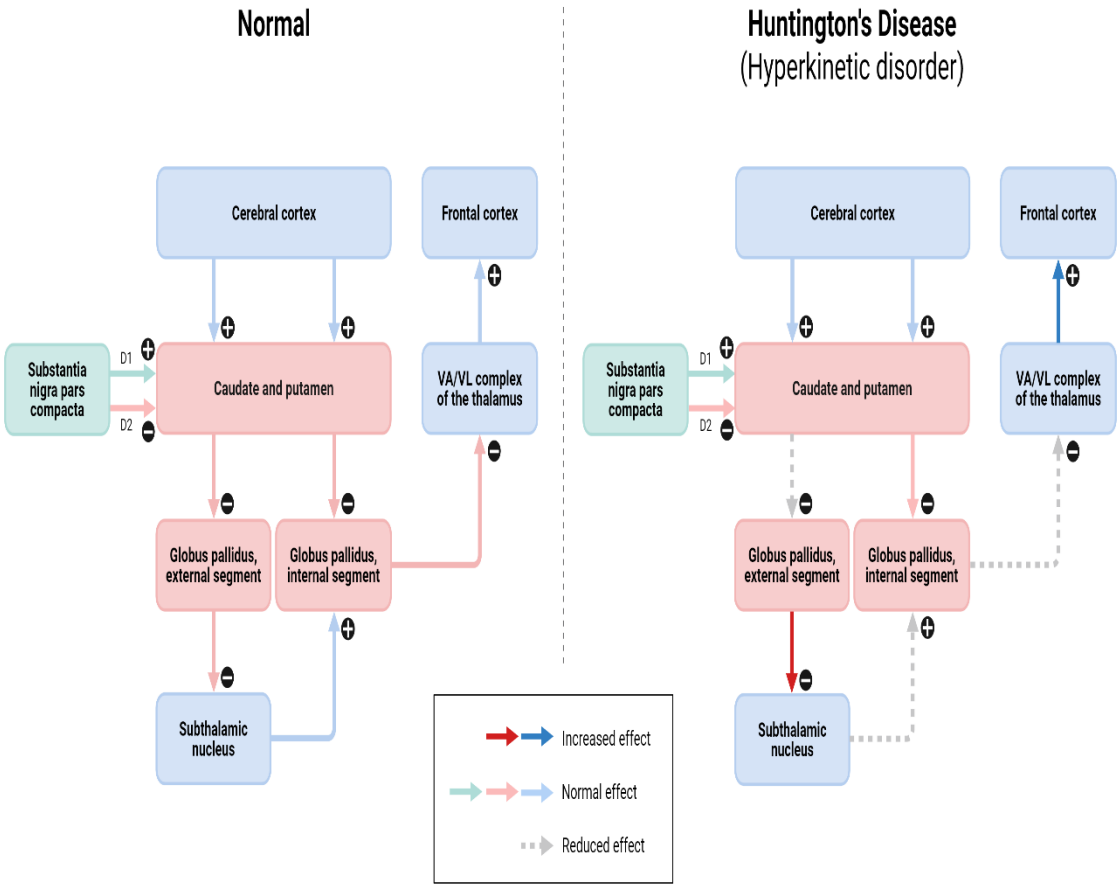

Figure 6. Pathophysiological of Huntington's disease.

Beyond their neurological benefits, coumarin derivatives have demonstrated significant cardioprotective and vasoregulatory properties[140]. Their well-known anticoagulant activity, exemplified by warfarin and its analogues, operates through inhibition of vitamin K epoxide reductase, thereby modulating blood coagulation and reducing thrombotic risk[141]. In addition to anticoagulation, newer coumarin derivatives exhibit potent vasodilatory, antihypertensive, and antiarrhythmic effects, often linked to the modulation of nitric oxide pathways and calcium channel regulation[142]. Experimental studies have shown that certain hydroxy- and methoxy-substituted coumarins can reduce myocardial oxidative stress, inhibit lipid peroxidation, and enhance cardiac mitochondrial function, collectively contributing to improved cardiac performance and reduced ischemia–reperfusion injury[143]. Furthermore, coumarins with antioxidant and anti-inflammatory profiles have been found to protect endothelial integrity, suppress platelet aggregation, and prevent atherosclerotic plaque formation[144]. Collectively, these findings position coumarin derivatives as promising scaffolds for the development of multifunctional cardiovascular agents that combine anticoagulant, vasoprotective, and antioxidant properties for comprehensive cardiac care.

6. Technological interfaces: Sensing, imaging, and delivery

Pharmaceutical compounds can be designed not only to achieve specific therapeutic outcomes but also to serve diagnostic and monitoring purposes[145]. Some molecules can function as probes in cellular and tissue imaging systems or as sensors for biomolecules that act as disease indicators[146]. Another promising strategy involves engineering drugs capable of targeted delivery—directing their activity toward a specific organ or tissue—to maximize therapeutic efficacy while minimizing systemic side effects[147]. Incorporating stimuli-responsive or triggering groups into these compounds enables them to be selectively activated at defined sites and times within the body, allowing precise spatial and temporal control over their pharmacological action[148].

Coumarin derivatives, in particular, possess intrinsic fluorescence properties, characterized by strong absorption and emission within the ultraviolet and visible light regions. This makes them excellent candidates for bioimaging applications. Their fluorescence can be modulated—often remaining weak under normal conditions but significantly enhanced upon interaction with specific biological targets—thus allowing selective visualization of disease-related processes[149]. Consequently, coumarin-based fluorophores have become widely used in the design of dyes and probes for cellular labeling and imaging[150]. These systems can selectively respond to biologically relevant analytes and exhibit superior photostability, high brightness, and minimal background fluorescence, enabling clear visualization of cell membranes, cytoplasm, and nuclei in complex biological environments[151].

Fluorescent probes and bioimaging

Coumarin derivatives are widely recognized for their versatility as fluorescent probes. Their utility in bioimaging primarily stems from two fundamental photophysical characteristics: the inherent fluorescence of the coumarin core and the modulation of fluorescence intensity in response to specific stimuli[152]. Depending on the system, these probes function as either “turn-on” or “turn-off” sensors, where fluorescence enhancement or quenching occurs following interaction with a target molecule or chemical process. The observed fluorescence arises mainly from intramolecular charge transfer transitions within the coumarin framework[153]. In general, coumarin probes incorporating electron-withdrawing substituents at the 3-position exhibit reduced baseline fluorescence. Upon interaction with a specific analyte that suppresses the intramolecular charge transfer process, a marked increase in fluorescence intensity is observed[154].

Among the various sensing systems developed, turn-on fluorescent probes targeting thiol-containing biomolecules such as cysteine and homocysteine are particularly prominent[155]. These probes typically integrate three functional elements: a coumarin fluorophore bearing an electron-withdrawing group, an N-acylhydrazone moiety serving as a thiol-reactive site, and a dye-silica nanocomposite platform for enhanced

sensing performance. When the N-acylhydrazone group reacts with cysteine or homocysteine, it cyclizes into a thiazolidine ring, effectively restoring fluorescence and imparting selectivity toward these biomolecules over glutathione[156]. Numerous variations on this molecular design have been reported to fine-tune sensitivity and selectivity across biological systems[157].

Beyond bioimaging, coumarins possess remarkable photophysical attributes that extend their applications into photodynamic and environmental domains[158]. Their high molar absorptivity in the UV–visible region and strong ability to quench singlet oxygen make them effective photoactive agents[159]. In photodynamic therapy and photocatalysis, coumarins contribute to the controlled removal of reactive oxygen species, thereby minimizing oxidative damage[160]. Furthermore, they serve as efficient photo-initiators in the synthesis of implantable polymeric materials, where their stability and photo-response are critical determinants of performance[161]. These multifaceted properties underscore the significance of coumarin-based systems in advancing both biomedical imaging and environmentally sustainable photochemical technologies[162].

Targeted delivery and prodrug strategies

Targeted drug delivery and prodrug strategies involving coumarin derivatives have emerged as powerful tools in modern medicinal chemistry, aiming to enhance therapeutic precision, reduce systemic toxicity, and improve pharmacokinetic profiles[163]. The intrinsic fluorescence, structural tunability, and biocompatibility of the coumarin scaffold make it an ideal platform for designing smart delivery systems that respond to specific physiological or pathological stimuli[164]. These strategies often employ coumarin as both a pharmacophore and a molecular reporter, allowing simultaneous drug tracking and controlled release within biological environments[165].

In targeted delivery systems, coumarin derivatives are frequently conjugated to nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, or silica-based systems[166]. These conjugates enable site-specific accumulation through passive mechanisms like the enhanced permeability and retention effect or through active targeting via receptor-mediated recognition[167]. Coumarin-based linkers or fluorogenic moieties incorporated within these systems provide dual functionality: they enable real-time imaging of the delivery process and ensure drug release in response to triggers such as pH, enzymatic activity, or redox potential. This integrated theranostic approach bridges therapy and diagnosis, providing valuable insight into drug biodistribution and efficacy *in vivo*[168].

Prodrug strategies involving coumarins have also gained considerable attention. In these systems, coumarin acts as a bioreversible masking group that can undergo enzymatic or chemical transformation at the target site to release the active drug[169]. The coumarin moiety can mask functional groups that would otherwise hinder bioavailability or cause premature metabolism. For instance, coumarin-linked prodrugs of anticancer or anti-inflammatory agents remain pharmacologically inactive until enzymatic cleavage by esterases or reductases within tumor or inflamed tissues triggers active drug liberation[170]. The inherent fluorescence of coumarin further allows monitoring of prodrug activation in real time, offering a unique advantage over traditional prodrug systems[171].

Overall, targeted delivery and prodrug design using coumarin scaffolds represent a convergence of chemistry, biology, and nanotechnology. These strategies not only optimize therapeutic efficacy and minimize off-target effects but also introduce a diagnostic dimension to pharmacotherapy[172]. Continued advances in coumarin chemistry are expected to yield next-generation drug delivery systems capable of precise spatial and temporal control, contributing significantly to the evolution of personalized and image-guided medicine[173].

7. Computational and theoretical perspectives

Computational approaches, when integrated with chemical intuition and experimental data, play a central role in the rational design of novel compounds. These methods not only identify feasible synthetic pathways but also predict potential biological activities and underlying mechanisms of action[174]. Among them, molecular docking is widely employed to characterize the probable binding interactions between coumarin derivatives and their biological targets[175]. Complementing this, quantitative SAR analyses enable the estimation of biological activity for newly designed compounds by correlating structural descriptors with known activities from a training dataset[176]. Furthermore, the emergence of artificial intelligence and machine learning tools has greatly enhanced the capacity to model reaction mechanisms and forecast plausible products in multi-step synthetic sequences[177].

Molecular docking, in particular, provides valuable insight into how modified coumarins interact with biomolecular targets at the atomic level. Docking platforms such as DockingWorld Web servers are often used to simulate and visualize these interactions. Such studies have elucidated coumarin binding modes with diverse targets, including proteins involved in antioxidant processes (e.g., stereoisomers of 3-bromothioridazine), viral entry and replication (e.g., interactions of 3-coumarinic acid esters with SARS-CoV-2 proteins), and antimicrobial defense mechanisms (e.g., associations between 6-arylcoumarins and bacterial membrane sterols)[178]. Building on these findings, quantitative SAR models developed for several Latin American coumarin derivatives have successfully established correlations between molecular architecture and biological efficacy, offering a predictive framework for the future design of more potent and selective bioactive molecules[179].

Molecular docking and quantitative SAR

SAR analysis and quantitative SAR modeling are essential computational tools in modern drug discovery. They facilitate the rational design and synthesis of novel bioactive molecules by correlating chemical structure with biological response and predicting molecular activity toward specific biological targets[180]. Complementary to these approaches, molecular docking provides a dynamic view of molecular recognition by simulating the interaction between ligands and their target macromolecules, thereby estimating binding affinities and identifying key residues involved in inhibition or activation[181]. Collectively, these computational methods streamline the design process, reduce experimental workload, and increase the likelihood of identifying promising lead compounds[182].

In the context of coumarin derivatives, such studies are instrumental in linking computational insights with practical synthesis. Typically, a curated set of coumarin analogues is docked against multiple receptors to establish correlations between structural features and biological activity. The computational outcomes not only help prioritize compounds for synthesis but also validate activity trends through comparison with experimental findings. The resulting pharmacophore models provide a conceptual framework for further *in silico* exploration and optimization[183]. Additionally, cost-effective quantitative SAR approaches—such as local regression surface modeling with shrinkage —enable the prediction of activity for newly designed analogues using established datasets[184]. When the 3D structure of the receptor's active site is available, advanced methods like rapid expansion diffusion quantum mechanics/molecular mechanics docking, integrated with the all-atom AMBER force field, can be employed to achieve highly accurate interaction profiles and energetics, guiding the next generation of bioactive coumarin derivatives[185].

Mechanistic modeling and reaction prediction

Density Functional Theory (DFT) provides a valuable computational framework for predicting chemical reactivity and elucidating plausible reaction mechanisms. By analyzing electronic density distributions, DFT-

based methods can rationalize reaction pathways and forecast product outcomes with significant accuracy[186]. For example, computational modeling can effectively predict the course of nucleophilic additions, such as those involving thiols attacking substituted α,β-unsaturated carbonyl systems[187]. In one study, a series of novel (*E*)-6-benzylidene-3,4-dihydroquinolin-2(1*H*)-one derivatives were synthesized, and their formation mechanisms were explored using DFT calculations[188]. Theoretical predictions closely matched the experimentally observed products, confirming the reliability of the proposed mechanism. Transition-state analyses further clarified the energetic preferences governing each reaction pathway, revealing the most favorable route for product formation[189].

Similarly, DFT modeling can elucidate cycloaddition reactions between α,β-unsaturated carbonyl compounds and substituted 1-[2-(1,3-benzothiazol-2-yl)ethylidene]-1*H*-indole-2,3-dione via a [3+2] cycloaddition process[190]. Computational insights enable the prediction of possible regioselectivities, depending on the reactive centers and the stabilization of the resulting adducts[191]. In some cases, the reaction may exhibit a bias toward forming the less thermodynamically stable product when side reactions, such as mercaptan interference, become kinetically significant. This highlights the predictive power of DFT in understanding complex organic transformations and optimizing reaction conditions accordingly[192].

8. Safety, toxicology, and ethical considerations

Safety considerations in the study and application of coumarin derivatives require a coordinated approach that integrates risk assessment and thorough toxicological characterization[193]. Naturally occurring coumarins are generally regarded as safe, and the use of plant-derived synthons in the synthesis of new derivatives further minimizes ecological impact. This is particularly true when hazardous reagents and organic solvents are replaced by environmentally benign alternatives[194]. Sustainability has therefore become a key design principle, especially in developing coumarin-based fluorescent probes for imaging and sensing applications[195]. Moreover, the same photophysical properties that make coumarins valuable as photodynamic therapy agents also necessitate careful evaluation of their phototoxic potential[196].

In line with modern ethical and regulatory standards, toxicological profiling and adherence to ethical guidelines are integral components of developing new bioactive coumarins. Reports describing their biological activity must include not only efficacy data but also detailed toxicity assessments—both for the compounds themselves and their potential metabolites[197]. Environmental implications related to their synthesis, application, and degradation should also be clearly addressed[198]. When coumarins are proposed as drug candidates, compliance with the "3Rs" principles—Replacement, Reduction, and Refinement—is essential. These guiding principles encourage minimizing animal testing through alternative experimental designs and prioritizing safer, more ethical research practices[199]. Furthermore, understanding the molecular mechanisms of coumarin activity can support the development of alternative therapeutic strategies, such as substituting antioxidant-based treatments when appropriate, thereby enhancing both safety and sustainability in coumarin research and development[200].

9. Conclusion

Coumarins and their derivatives continue to represent a bridge between synthetic chemistry and biological innovation, embodying a versatile class of compounds with exceptional pharmacological, photophysical, and technological potential. Their benzopyran-2-one scaffold provides a chemically flexible platform that allows for targeted structural modifications, enabling the design of multifunctional molecules with applications ranging from therapeutics and diagnostics to materials science. Advances in synthetic methodologies—including green chemistry protocols, catalytic transformations, and microwave-assisted reactions—have not

only streamlined coumarin production but also aligned it with the global shift toward sustainable and eco-friendly chemical practices.

The biological diversity of coumarins encompasses anticancer, antimicrobial, antiviral, antifungal, neuroprotective, and cardioprotective activities, all of which are closely related to their electronic configuration and substitution patterns. Computational tools such as molecular docking, quantitative SAR modeling, and DFT calculations have further enhanced understanding of their structure–function relationships, accelerating the rational design of potent and selective derivatives. Moreover, their intrinsic fluorescence has expanded their role into imaging, sensing, and photodynamic applications, offering a unique interface between biology and technology. Future research must continue integrating synthetic innovation with biological insight and computational prediction. A stronger emphasis on safety, ethical responsibility, and environmental stewardship could ensure that the next generation of coumarin-based compounds remains not only effective but also sustainable and ethically produced. By uniting advances in chemistry, biology, and data-driven modeling, coumarins stand poised to drive the next wave of progress in drug discovery, bioengineering, and applied chemical sciences, firmly establishing their status as privileged scaffolds at the interface of modern science and technology.

Conflict of interest

The authors declare no conflict of interest.

References

1. Fernández-Torras A, Comajuncosa-Creus A, Duran-Frigola M, Aloy P. Connecting chemistry and biology through molecular descriptors. Current Opinion in Chemical Biology. 2022;66:102090.
2. Zeki NM, Mustafa YF. 6,7-Coumarin-heterocyclic hybrids: A comprehensive review of their natural sources, synthetic approaches, and bioactivity. Journal of Molecular Structure. 2024;1303:137601.
3. Mustafa YF. Effects of heat variables on the starch content of cooked white rice: Searching for diabetes-friendly food. Bioactive Carbohydrates and Dietary Fibre. 2024;31:100395.
4. Mustafa YF. Bioactive Coumarins: Bioorganic Strategies for Targeting Enzymes, Receptors, and DNA. Russian Journal of Bioorganic Chemistry. 2025;51(5):2304–35.
5. Mustafa YF. Coumarins at the Crossroads of Drug Development: Enzyme Modulation for Clinical Advances. Indian Journal of Clinical Biochemistry. 2025; https://doi.org/10.1007/s12291-025-01331-2
6. Xia D, Liu H, Cheng X, Maraswami M, Chen Y, Lv X. Recent Developments of Coumarin-based Hybrids in Drug Discovery. Current Topics in Medicinal Chemistry. 2022;22(4):269–83.
7. Oglah MK, Mustafa YF. Synthesis, antioxidant, and preliminary antitumor activities of new curcumin analogues. Journal of Global Pharma Technology. 2020;12(2):854–62.
8. Mustafa YF. Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues. Journal of Global Pharma Technology. 2019;11(9):1–10.
9. Mishra S, Pandey A, Manvati S. Coumarin: An emerging antiviral agent. Heliyon. 2020;6(1):e03217.
10. Jebir RM, Mustafa YF. Natural products catalog of allsweet watermelon seeds and evaluation of their novel coumarins as antimicrobial candidates. Journal of Medicinal and Chemical Sciences. 2022;5(5):831–47.
11. Xu X, Shi Y, Yu Q, Peng Y, Zhao F, Cui J, Chen Y, Liu L, Zhang Y, Zhang J, Wei B. Coumarin-derived imino sulfonate 5h ameliorates cardiac injury induced by myocardial infarction via activating the Sirt1/Nrf2 signaling pathway. European Journal of Pharmacology. 2023;945:175615.
12. Mustafa YF. Mechanistic insights into the anti-obesity actions of coumarins: Therapeutic potential and future directions. Obesity Medicine. 2025;55:100620.
13. Al-Shakarchi W, Mustafa YF. Coumarins in the human–nature nexus: Exploring their environmental and psychological footprint. Environment and Social Psychology. 2025;10(4):3641.
14. Mahmood AT, Kamal IK, Mustafa YF. Coumarins as Emerging Agents in Neurodegenerative Disease Management. Russian Journal of Bioorganic Chemistry. 2025;51(5):2228–46.
15. Rajabi M, Feyzbakhsh H. Polymeric nanocarriers in drug delivery, bioimaging, and biosensing: advances and perspectives on nanomicelles, nanogels, and dendrimers. RSC Advances. 2025;15(48):40400–38.
16. Jasim SF, Mustafa YF. Beyond coumarin: the rise of benzocoumarins in chemical and biomedical sciences. Chemical Papers. 2025;
17. Mohammed Alshaher M, Fakri Mustafa Y. From laboratory to computer models: Enhancing coumarin discovery through interdisciplinary research. Applied Chemical Engineering. 2025;8(1):1–19.

18. Stefanachi A, Leonetti F, Pisani L, Catto M, Carotti A. Coumarin: A Natural, Privileged and Versatile Scaffold for Bioactive Compounds. Molecules. 2018;23(2):250.
19. Mustafa YF, Hassan DA. Dioxolocoumarins: Bridging chemistry and pharmacology with multifunctional therapeutics. Applied Chemical Engineering. 2024;7(4):ACE-5592.
20. Jebir RM, Mustafa YF. Watermelon Allsweet: A promising natural source of bioactive products. Journal of Medicinal and Chemical Sciences. 2022;5(5):652–66.
21. Vigueras G, Izquierdo-García E, de la Torre-Rubio E, Abad-Montero D, Santana MD, Marchán V, Ruiz J. Metal–coumarin derivatives as promising photosensitizers: unlocking their cancer phototherapy potential. Inorganic Chemistry Frontiers. 2025;
22. Mustafa YF. Coumarins derived from natural methoxystilbene as oxidative stress-related disease alleviators: Synthesis and in vitro-in silico study. Journal of Molecular Structure. 2024;1302:137471.
23. El-Sawy ER, Abdelwahab AB, Kirsch G. Synthetic Routes to Coumarin(Benzopyrone)-Fused Five-Membered Aromatic Heterocycles Built on the α-Pyrone Moiety. Part 1: Five-Membered Aromatic Rings with One Heteroatom. Molecules. 2021;26(2):483.
24. Waheed SA, Mustafa YF. Novel naphthalene-derived coumarin composites: synthesis, antibacterial, and antifungal activity assessments. Eurasian Chemical Communications. 2022;4(8):709–24.
25. Patra I, Ansari MJ, Saadoon N, Mashhadani ZI Al, Obaid NH, Alawsi T, Jabbar AH, Mustafa YF. Insights into the Electronic Properties of Coumarins: A Comparative Study Photocatalytic Degradation of Methylene Blue. Physical Chemistry Research. 2023;11(2):437–47.
26. Jibroo RN, Mustafa YF, Al-Shakarchi W. Heterocycles fused on a 6,7-coumarin framework: an in-depth review of their structural and pharmacological diversity. Chemical Papers. 2024;78:7239–7311.
27. Mustafa YF, Faisal AF, Alshaher MM, Hassan DA. Food-Derived Micronutrients as Alleviators of Age-Related Dysfunction: A Dive into Their Effects and Cellular Mechanisms. Indian Journal of Clinical Biochemistry. 2025;40(3):322–38.
28. Ge C, Pei F, Wang X, Zhang P, Li H, Sai Z, Yang Y, Chang K, Ni T, Yang Z. Coumarin-based fluorescent probes for the detection of copper (II) and imaging in mice of Wilson's disease. Bioorganic Chemistry. 2025;154:108051.
29. Ortega-Forte E, Rovira A, Gandioso A, Bonelli J, Bosch M, Ruiz J, Marchán V. COUPY Coumarins as Novel Mitochondria-Targeted Photodynamic Therapy Anticancer Agents. Journal of Medicinal Chemistry. 2021;64(23):17209–20.
30. Mustafa YF. Triple coumarin-based 5-fluorouracil prodrugs, their synthesis, characterization, and release kinetics. Journal of Molecular Structure. 2024;1301:137415.
31. Mustafa YF, Bashir MK, Oglah MK. Original and innovative advances in the synthetic schemes of coumarin-based derivatives: A review. Systematic Reviews in Pharmacy. 2020;11(6):598–612.
32. Mustafa YF, Kasim SM, Al-Dabbagh BM, Al-Shakarchi W. Synthesis, characterization and biological evaluation of new azo-coumarinic derivatives. Applied Nanoscience (Switzerland). 2023;13:1095–1102.
33. Şeker Karatoprak G, Dumlupınar B, Celep E, Kurt Celep I, Küpeli Akkol E, Sobarzo-Sánchez E. A comprehensive review on the potential of coumarin and related derivatives as multi-target therapeutic agents in the management of gynecological cancers. Frontiers in Pharmacology. 2024;15:1423480.
34. Xiao Z, Chen D, Song S, van der Vlag R, van der Wouden PE, van Merkerk R, Cool RH, Hirsch AKH, Melgert BN, Quax WJ, Poelarends GJ, Dekker FJ. 7-Hydroxycoumarins Are Affinity-Based Fluorescent Probes for Competitive Binding Studies of Macrophage Migration Inhibitory Factor. Journal of Medicinal Chemistry. 2020;63(20):11920–33.
35. Jasim SF, Mustafa YF. A Review of Classical and Advanced Methodologies for Benzocoumarin Synthesis. Journal of Medicinal and Chemical Sciences. 2022;5(5):676–94.
36. Fernández-Peña L, Matos MJ, López E. Recent Advances in Biologically Active Coumarins from Marine Sources: Synthesis and Evaluation. Marine Drugs. 2022;21(1):37.
37. Mustafa YF. Coumarins from nature to nurture: A sustainable resource for drug discovery and beyond. Applied Chemical Engineering. 2025;8(2):5676.
38. Mustafa YF. Coumarin derivatives in pharmaceutical and biomedical engineering: Advances in design, synthesis, and therapeutic applications. Applied Chemical Engineering. 2025;8(3):5728.
39. Annunziata F, Pinna C, Dallavalle S, Tamborini L, Pinto A. An overview of coumarin as a versatile and readily accessible scaffold with broad-ranging biological activities. International Journal of Molecular Sciences. 2020;21(13):1–83.
40. Mustafa YF. Integrating chemical engineering approaches in the biomedical utilization of coumarin derivatives. Applied Chemical Engineering. 2025;8(3):5739.
41. Waheed SA, Mustafa YF. Synthesis and evaluation of new coumarins as antitumor and antioxidant applicants. Journal of Medicinal and Chemical Sciences. 2022;5(5):808–19.
42. Yasin G, Jasim SA, Raya I, Kzar HH, Abed Hussein B, Al-Gazally ME, Ahmed YM, Altimari US, Alkaim AF, Fakri Mustafa Y. Computational Study of Interaction and Removal of Benzopyran by Anatase Titanium Dioxide Nanoparticle. Polycyclic Aromatic Compounds. 2023;43(5):4467–77.

43. Niinivehmas S, Pentikäinen O. Coumarins as Tool Compounds to Aid the Discovery of Selective Function Modulators of Steroid Hormone Binding Proteins. Molecules. 2021;26(17):5142.
44. Mustafa YF. Combretastatin A4-based coumarins: synthesis, anticancer, oxidative stress-relieving, anti-inflammatory, biosafety, and in silico analysis. Chemical Papers. 2024;78:3705–3720.
45. Mustafa YF. Biocompatible chlorocoumarins from harmful chlorophenols, their synthesis and biomedicinal evaluation. Journal of Molecular Structure. 2024;1309:138193.
46. Raya I, Danshina S, Jalil AT, Suksatan W, Mahmoud MZ, Roomi AB, Mustafa YF, Kazemnejadi M. Catalytic filtration: efficient C-C cross-coupling using Pd(II)-salen complex-embedded cellulose filter paper as a portable catalyst. RSC Advances. 2022;12(31):20156–73.
47. Worch JC, Stubbs CJ, Price MJ, Dove AP. Click Nucleophilic Conjugate Additions to Activated Alkynes: Exploring Thiol-yne, Amino-yne, and Hydroxyl-yne Reactions from (Bio)Organic to Polymer Chemistry. Chemical Reviews. 2021;121(12):6744–76.
48. Mustafa YF, Hassan DA, Faisal AF, Alshaher MM. Synthesis of novel skipped diene-3-halocoumarin conjugates as potent anticancer and antibacterial biocompatible agents. Results in Chemistry. 2024;11:101846.
49. Lu WY, Wang Y, You Y, Wang ZH, Zhao JQ, Zhou MQ, Yuan WC. Copper-Catalyzed Decarboxylative [3 + 2] Annulation of Ethynylethylene Carbonates with Azlactones: Access to γ-Butyrolactones Bearing Two Vicinal Quaternary Carbon Centers. The Journal of Organic Chemistry. 2021;86(2):1779–88.
50. Mustafa YF, Bashir MK, Oglah MK. Influence of albocarbon-cyclic hybridization on biomedical activities: A review. Journal of Medicinal and Chemical Sciences. 2022;5(4):518–35.
51. Kasim SM, Al-Bazzaz FY, Hammoodi SH, Mustafa YF. A review of Schiff base-inorganic complexes and recent advances in their biomedicinal and catalytic attributes. Eurasian Chemical Communications. 2023;5(6):522–35.
52. Mustafa YF. 4-Chloroskimmetine-based derivatives as potential anticancer and antibacterial prospects: Their synthesis and in vitro inspections. Results in Chemistry. 2024;7:101511.
53. Kumar S, Jyoti J, Gupta D, Singh G, Kumar A. A Decade of Exploration of Transition-Metal-Catalyzed Cross-Coupling Reactions: An Overview. SynOpen. 2023;07(04):580–614.
54. Díez-Poza C, Álvarez-Miguel L, Mosquera MEG, Whiteoak CJ. Synthesis and applications of the sulfur containing analogues of cyclic carbonates. Organic & Biomolecular Chemistry. 2023;21(18):3733–55.
55. Zeki NM, Mustafa YF. Annulated Heterocyclic[g]Coumarin Composites: Synthetic Approaches and Bioactive Profiling. Chemistry and Biodiversity. 2024;21(3):e202301855.
56. Saini P, Jyoti, Sharma PK, Singh V. β-halovinyl Aldehydes: Multifaceted Versatile Building Blocks In Organic Synthesis. European Journal of Organic Chemistry. 2025;28(6):e202401058.
57. Tiwari G, Khanna A, Mishra VK, Sagar R. Recent developments on microwave-assisted organic synthesis of nitrogen- and oxygen-containing preferred heterocyclic scaffolds. RSC Advances. 2023;13(47):32858–92.
58. Mustafa YF. Synthesis of novel 6-aminocoumarin derivatives as potential –biocompatible antimicrobial and anticancer agents. Journal of Molecular Structure. 2025;1320:139658.
59. Riadi Y, M. Kadhim M, Jawad Shoja S, Hussein Ali M, Fakri Mustafa Y, Sajjadi A. Copper (II) complex supported on the surface of magnetic nanoparticles modified with S-benzylisothiourea (Fe 3 O 4 @SiO 2 -SMTU-Cu): A new and efficient nanomagnetic catalyst for the synthesis of quinazolines and amides. Synthetic Communications. 2022;52(6):875–87.
60. Raya I, Altimari US, Alami BG, Srikanth S, Gatea MA, Romero-Parra RM, Barboza-Arenas LA, Mustafa YF. A green and sustainable selective oxidation of aromatic sulfides to sulfoxides derivatives via graphite electro-catalysed reaction with sodium bromide. Journal of Molecular Structure. 2023;1293:136271.
61. Raya I, Chupradit S, Kadhim MM, Mahmoud MZ, Jalil AT, Surendar A, Ghafel ST, Mustafa YF, Bochvar AN. Role of Compositional Changes on Thermal, Magnetic and Mechanical Properties of Fe-P-C-Based Amorphous Alloys. Chinese Physics B. 2022;31(1):016401.
62. Dunås P, Murfin LC, Nilsson OJ, Jame N, Lewis SE, Kann N. Azulene Functionalization by Iron-Mediated Addition to a Cyclohexadiene Scaffold. The Journal of Organic Chemistry. 2020;85(21):13453–65.
63. Jibroo RN, Mustafa YF, Al-Shakarchi W. Synthesis and evaluation of linearly fused thiadiazolocoumarins as prospects with broad-spectrum bioactivity. Results in Chemistry. 2024;7:101494.
64. Mustafa YF. Biocompatible new coumarins as dual-target anti-inflammatory agents: Insights from chemistry to toxicity. Next Research. 2025;2(2):100236.
65. Saxena A, Shastri L, Sunagar V. Green approach for the synthesis of 4-coumarin-4 H -pyrans from 4-formylcoumarins and their antibacterial study. Synthetic Communications. 2017;47(17):1570–6.
66. Noroozi-Shad N, Gholizadeh M, Sabet-Sarvestani H. Quaternary phosphonium salts in the synthetic chemistry: Recent progress, development, and future perspectives. Journal of Molecular Structure. 2022;1257:132628.
67. Kadam PR, Bodke YD, Naik MD, Nagaraja O, Manjunatha B. One-pot three-component synthesis of thioether linked 4-hydroxycoumarin-benzothiazole derivatives under ambient condition and evaluation of their biological activity. Results in Chemistry. 2022;4:100303.
68. Ismael RN, Mustafa YF, Al-qazaz HK. Citrullus lanatus, a Potential Source of Medicinal Products : A Review. Journal of Medicinal and Chemical Sciences. 2022;5(4):607–18.

69. Mustafa YF. Coumarins in Traditional Medicine: Bridging Ancient Wisdom and Scientific Progress. Phytomedicine Plus. 2025;5(3):100857.
70. Mustafa YF. Applications of artificial intelligence in the synthesis, docking, and pharmacological profiling of coumarins. Applied Chemical Engineering. 2025;8(2):5678.
71. Faisal AF, Mustafa YF. Isolation of unique fluorinated coumarins from new mexico green chile seeds : a novel green extraction approach and bioevaluation against oxidative stress disorders. Food Chemistry Advances. 2025;8:101057.
72. Younes AH, Mustafa YF. Novel coumarins from green sweet bell pepper seeds: Their isolation, characterization, oxidative stress-mitigating, anticancer, anti-inflammatory, and antidiabetic properties. Journal of Molecular Structure. 2024;1312:138629.
73. Abdulaziz NT, Mustafa YF. Antibacterial and Antitumor Potentials of Some Novel Coumarins. International Journal of Drug Delivery Technology. 2022;12(1):239–47.
74. Jasim SF, Mustafa YF. New fused-coumarin composites: Synthesis, anticancer and antioxidant potentials evaluation. Eurasian Chemical Communications. 2022;4(7):607–19.
75. Kourat O, Benhalima N, Al-Dies AAM, Guendouzi A, Benyahlou ZD, Megrouss Y, Drissi M, Alem GA, Sindi ER, Zaki MEA. Structural, nonlinear optical, and molecular docking studies of schiff base compounds as multi-target inhibitors of AChE, BChE, and carbonic anhydrases. Scientific Reports. 2025;15(1):34818.
76. Zeki NM, Mustafa YF. Coumarin hybrids for targeted therapies: A promising approach for potential drug candidates. Phytochemistry Letters. 2024;60:117–33.
77. Chamsaz EA, Sun S, Maddipatla MVSN, Joy A. Photoresponsive polyesters by incorporation of alkoxyphenacyl or coumarin chromophores along the backbone. Photochemical & Photobiological Sciences. 2014;13(2):412–21.
78. Nejres AM, Mustafa YF, Aldewachi HS. Evaluation of natural asphalt properties treated with egg shell waste and low density polyethylene. International Journal of Pavement Engineering. 2022;23(1):39–45.
79. Evangelista E, de Jesus IS, Pauli FP, de Souza AS, Borges A de A, Gomes MVSF, Ferreira VF, da Silva F de C, Melo MA, Forezi L da SM. Recent Advances in the Application of Coumarins as Photosensitizers for the Construction of a Dye-Sensitized Solar Cell. ACS Omega. 2025;10(14):13726–48.
80. Mustafa YF. Synthesis of 7,8-dihydroxy-4-phenylbenzo[g]coumarins as potential multitarget anti-skin-aging candidates. Journal of Molecular Structure. 2025;1321:139806.
81. Shaydyuk YO, Bashmakova N V., Klishevich G V., Dmytruk AM, Kachkovsky OD, Kuziv IB, Dubey IY, Belfield KD, Bondar M V. Nature of Linear Spectral Properties and Fast Relaxations in the Excited States and Two-Photon Absorption Efficiency of 3-Thiazolyl and 3-Phenyltiazolyl Coumarin Derivatives. ACS Omega. 2023;8(12):11564–73.
82. Ma M, Luo L, Liu L, Ding Y, Dong Y, Fang B. Synthesis of Coumarin-Based Photosensitizers for Enhanced Antibacterial Type I/II Photodynamic Therapy. Molecules. 2024;29(16):3793.
83. Paul S, Roy P, Das S, Ghosh S, Sardar PS, Majhi A. Addressing the Exigent Role of a Coumarin Fluorophore toward Finding the Suitable Microenvironment of Biomimicking and Biomolecular Systems: Steering to Project the Drug Designing and Drug Delivery Study. ACS Omega. 2021;6(18):11878–96.
84. Rajasekar M, Mary J, Sivakumar M, Selvam M. Recent developments in sunscreens based on chromophore compounds and nanoparticles. RSC Advances. 2024;14(4):2529–63.
85. Li Z, Kong D, Liu Y, Li M. Pharmacological perspectives and molecular mechanisms of coumarin derivatives against virus disease. Genes & diseases. 2022;9(1):80–94.
86. Zeki NM, Mustafa YF. Novel heterocyclic coumarin annulates: synthesis and figuring their roles in biomedicine, bench-to-bedside investigation. Chemical Papers. 2024;78:4935–51.
87. Mustafa YF. Nutraceutical-based telomerase inhibitors: Renewed hope for cancer therapy. Phytomedicine Plus. 2024;4(2):100537.
88. Zeki NM, Mustafa YF. Natural linear coumarin-heterocyclic conjugates: A review of their roles in phytotherapy. Fitoterapia. 2024;175:105929.
89. Younes AH, Mustafa YF. Plant-Derived Coumarins: A Narrative Review Of Their Structural And Biomedical Diversity. Chemistry & Biodiversity. 2024;21(6):e202400344.
90. Naeem N, Sadiq A, Othman GA, Yassin HM, Mughal EU. Exploring heterocyclic scaffolds in carbonic anhydrase inhibition: a decade of structural and therapeutic insights. RSC Advances. 2024;14(48):35769–970.
91. Zeki NM, Mustafa YF. Coumarin hybrids: a sighting of their roles in drug targeting. Chemical Papers. 2024;78:5753–5772.
92. Abdulaziz NT, Mohammed ET, Khalil RR, Mustafa YF. Unrevealing the total phenols, total flavonoids, antioxidant, anti-inflammatory, and cytotoxic effects of Garden Cress seed ethanolic extracts. Review of Clinical Pharmacology and Pharmacokinetics - International Edition. 2024;38(2):187–96.
93. Lončarić M, Strelec I, Pavić V, Šubarić D, Rastija V, Molnar M. Lipoxygenase Inhibition Activity of Coumarin Derivatives—QSAR and Molecular Docking Study. Pharmaceuticals. 2020;13(7):154.
94. Zeki MN, Mustafa YF. Synthesis and evaluation of novel ring-conjugated coumarins as biosafe broad-spectrum antimicrobial candidates. Journal of Molecular Structure. 2024;1309:138192.

95. Abdulaziz NT, Al-bazzaz FY, Mustafa YF. Natural products for attenuating Alzheimer's disease: A narrative review. Eurasian Chemical Communications. 2023;5(4):358–70.
96. Sobhy MK, Mowafy S, Lasheen DS, Farag NA, Abouzid KAM. 3D-QSAR pharmacophore modelling, virtual screening and docking studies for lead discovery of a novel scaffold for VEGFR 2 inhibitors: Design, synthesis and biological evaluation. Bioorganic Chemistry. 2019;89:102988.
97. Al-Shakarchi W, Abdulaziz NT, Mustafa YF. A review of the chemical, pharmacokinetic, and pharmacological aspects of quercetin. Eurasian Chemical Communications. 2022;4(7):645–56.
98. Mustafa YF. 3-mercaptocoumarins as potential bioactive candidates: From novel synthesis to comparative analysis. Journal of Molecular Structure. 2025;1320:139657.
99. Singh H, Singh JV, Bhagat K, Gulati HK, Sanduja M, Kumar N, Kinarivala N, Sharma S. Rational approaches, design strategies, structure activity relationship and mechanistic insights for therapeutic coumarin hybrids. Bioorganic & Medicinal Chemistry. 2019;27(16):3477–510.
100. Yakkala PA, Kamal A. Dual-targeting inhibitors involving tubulin for the treatment of cancer. Bioorganic Chemistry. 2025;156:108116.
101. Younes AH, Mustafa YF. Unveiling the Biomedical Applications of Novel Coumarins Isolated From Capsicum Annuum L. Seeds by a Multivariate Extraction Technique. Chemistry and Biodiversity. 2024;21(6):e202400581.
102. MUSA MA, BADISA VLD, LATINWO LM, NTANTIE E. 7,8-Dihydroxy-3-arylcoumarin Induces Cell Death Through S-Phase Arrest in MDA-MB-231 Breast Cancer Cells. Anticancer Research. 2018;38(11):6091–8.
103. Mustafa YF. Coumarins from toxic phenol: An algorithm of their synthesis and assessment as biosafe, wide-spectrum, potent antimicrobial prospects. Applied Chemical Engineering. 2024;7(3):5527.
104. Jibroo RN, Mustafa YF. Linearly ring-fused coumarins: A review of their cancer-fighting attributes. Results in Chemistry. 2024;8:101611.
105. Zamanian MY, Parra RMR, Soltani A, Kujawska M, Mustafa YF, Raheem G, Al-Awsi L, Lafta HA, Taheri N, Heidari M, Golmohammadi M, Bazmandegan G. Targeting Nrf2 signaling pathway and oxidative stress by resveratrol for Parkinson's disease: an overview and update on new developments. Molecular Biology Reports. 2023;50:5455–5464.
106. Khalil RR, Mohammed ET, Mustafa YF. Various promising biological effects of Cranberry extract: A review. Clinical Schizophrenia and Related Psychoses. 2021;15(S6):1–9.
107. Pillai VM, Sreejaya MM, C P A, M H, Murali A, K K H, Bera M, Gangopadhyay M. A perspective on the stimuli-responsive photoactivities of coumarin with a focus on redox-responsive photodynamic therapy (PDT). Dyes and Pigments. 2024;224:112006.
108. Bonelli J, Ortega-Forte E, Rovira A, Bosch M, Torres O, Cuscó C, Rocas J, Ruiz J, Marchán V. Improving Photodynamic Therapy Anticancer Activity of a Mitochondria-Targeted Coumarin Photosensitizer Using a Polyurethane–Polyurea Hybrid Nanocarrier. Biomacromolecules. 2022;23(7):2900–13.
109. Mustafa YF. Natural immune boosters: coumarins as emerging potentiators of immunity in drug discovery. Phytomedicine Plus. 2025;5(4):100880.
110. Mustafaa YF. New Coumarin-Metronidazole Composites: Synthesis, Biocompatibility, and Anti-anaerobic Bacterial Activity. Russian Journal of Bioorganic Chemistry. 2024;50(1):201–10.
111. Huang CC, Chang KH, Chiu YJ, Chen YR, Lung TH, Hsieh-Li HM, Su MT, Sun YC, Chen CM, Lin W, Lee-Chen GJ. Multi-Target Effects of Novel Synthetic Coumarin Derivatives Protecting Aβ-GFP SH-SY5Y Cells against Aβ Toxicity. Cells. 2021;10(11):3095.
112. Kamal IK, Mahmood AT, Mustafa YF. Synthesis of Eugenol-Derived Coumarins as Broad-Spectrum Biosafe Antimicrobial Agents. Russian Journal of Bioorganic Chemistry. 2024;50(6):2240–51.
113. Mahmood AT, Kamal IK, Mustafa YF. Coumarin Backbone as a Door-Opening Key for Investigating Chloroxylenol as Oral Antimicrobial Agents: an In Vitro–In Silico Study. Russian Journal of Bioorganic Chemistry. 2024;50(6):2252–68.
114. Kolodziejczyk-Czepas J, Czepas J. Plant-Derived Compounds and Extracts as Modulators of Plasmin Activity—A Review. Molecules. 2023;28(4):1677.
115. Koley M, Han J, Soloshonok VA, Mojumder S, Javahershenas R, Makarem A. Latest developments in coumarin-based anticancer agents: mechanism of action and structure–activity relationship studies. RSC Medicinal Chemistry. 2024;15(1):10–54.
116. Kasim SM, Abdulaziz NT, Jasim MH, Mustafa YF. Resveratrol in cancer chemotherapy: Is it a preventer, protector, or fighter? Eurasian Chemical Communications. 2023;5(7):576–87.
117. Al Abdeen SHZ, Mustafa YF, Mutlag SH. Synthesis and biomedical activities of novel multifunctional benzodipyrone-based derivatives. Eurasian Chemical Communications. 2022;4(10):938–49.
118. Li M, Cao F, Wang W, Ma Y, Yu Z, Wang K, Chen Y, Liu H. Coumarin–Furoxan Hybrid Suppressed the Proliferation and Metastasis of Triple-Negative Breast Cancer by Activating Mitochondrial Stress and Cell Apoptosis. ACS Pharmacology & Translational Science. 2024;7(5):1278–90.
119. Huang HT, Huang CY, Lee CJ, Sun BJ, Jhang ZW, Wen CC, Wang YH, Li TS, Chern CY, Chen YH. The angiogenesis-modulating effects of coumarin-derivatives. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology. 2024;278:109862.

120. Zeki NM, Mustafa YF. Digital alchemy: Exploring the pharmacokinetic and toxicity profiles of selected coumarin-heterocycle hybrids. Results in Chemistry. 2024;10:101754.
121. Mustafa YF, Jebir RM. Plant-derived extracts and conventional drugs : A new frontier in antimicrobial therapy. Journal of Herbmed Pharmacology. 2025;14(2):163–87.
122. Faisal AF, Mustafa YF. Capsicum in Clinical Biochemistry: Insights into its Role in Health and Disease. Indian Journal of Clinical Biochemistry. 2025; https://doi.org/10.1007/s12291-025-01317-0
123. Lafitte D, Lamour V, Tsvetkov PO, Makarov AA, Klich M, Deprez P, Moras D, Briand C, Gilli R. DNA Gyrase Interaction with Coumarin-Based Inhibitors: The Role of the Hydroxybenzoate Isopentenyl Moiety and the 5'-Methyl Group of the Noviose. Biochemistry. 2002;41(23):7217–23.
124. Malviya J, Alameri AA, Al-Janabi SS, Fawzi OF, Azzawi AL, Obaid RF, Alsudani AA, Alkhayyat AS, Gupta J, Mustafa YF, Karampoor S, Mirzaei R. Metabolomic profiling of bacterial biofilm: trends, challenges, and an emerging antibiofilm target. World Journal of Microbiology and Biotechnology. 2023;39(8):212.
125. Alshaher MM, Mustafa YF. Linear pyranocoumarins are potential dazzling dancers between nature, chemistry, and clinical application. Vol. 5, Phytomedicine Plus. 2025. p. 100785.
126. Alshaher MM, Mustafa YF. Synthesis of triclosan-derived coumarins as potent, biocompatible, broad-spectrum antimicrobial agents. Applied Chemical Engineering. 2024;7(4):5579.
127. Sharapov AD, Fatykhov RF, Khalymbadzha IA, Zyryanov G V., Chupakhin ON, Tsurkan M V. Plant Coumarins with Anti-HIV Activity: Isolation and Mechanisms of Action. Vol. 24, International Journal of Molecular Sciences. 2023.
128. Hassan DA, Mustafa YF. Linear furanocoumarins: Bridging natural wisdom and synthetic ingenuity in drug discovery. Phytomedicine Plus. 2025;5:100832.
129. Mali G, Maji S, Chavan KA, Shukla M, Kumar M, Bhattacharyya S, Erande RD. Effective Synthesis and Biological Evaluation of Functionalized 2,3-Dihydrofuro[3,2- c]coumarins via an Imidazole-Catalyzed Green Multicomponent Approach. ACS Omega. 2022;7(40):36028–36.
130. Alandijany TA, El-Daly MM, Tolah AM, Bajrai LH, Khateb AM, Alsaady IM, Altwaim SA, Dubey A, Dwivedi VD, Azhar EI. Investigating the Mechanism of Action of Anti-Dengue Compounds as Potential Binders of Zika Virus RNA-Dependent RNA Polymerase. Viruses. 2023;15(7):1501.
131. Mustafa YF. New Coumarin Hybrids from Chloramphenicol: A Step Towards Next-Generation Biocompatible Antimicrobials. Russian Journal of Bioorganic Chemistry. 2025;51(5):2274–87.
132. Faisal AF, Mustafa YF. Chili pepper: A delve into its nutritional values and roles in food-based therapy. Food Chemistry Advances. 2025;6:100928.
133. Alves AMCV, Cruz-Martins N, Rodrigues CF. Marine Compounds with Anti-Candida sp. Activity: A Promised "Land" for New Antifungals. Journal of Fungi. 2022;8(7):669.
134. Faisal AF, Mustafa YF. The Multifaceted Chemistry of Chili Peppers: A Biodiversity Treasure for Nutrition and Biomedicine. Chemistry & Biodiversity. 2025;e202402690.
135. Prusty JS, Kumar A. Coumarins: antifungal effectiveness and future therapeutic scope. Molecular Diversity. 2020;24(4):1367–83.
136. Zeki NM, Mustafa YF. Synthesis of Novel Dioxathiole-6,7-coumarin Hybrids As Cytosafe-Multifunctional Applicants: An In Vitro—In Silico Study. Russian Journal of Bioorganic Chemistry. 2024;50(5):2076–91.
137. Younes HA, Mustafa YF. Sweet Bell Pepper: A Focus on Its Nutritional Qualities and Illness-Alleviated Properties. Indian Journal of Clinical Biochemistry. 2024;39:459–69.
138. Al-Rashidi RR, Noraldeen SAM, Kareem AK, Mahmoud AK, Kadhum WR, Ramírez-Coronel AA, Iswanto AH, Obaid RF, Jalil AT, Mustafa YF, Nabavi N, Wang Y, Wang L. Malignant function of nuclear factor-kappaB axis in prostate cancer: Molecular interactions and regulation by non-coding RNAs. Pharmacological Research. 2023;194:106775.
139. Kasim SM, Al-Dabbagh BM, Mustafa YF. A review on the biological potentials of carbazole and its derived products. Eurasian Chemical Communications. 2022;4(6):495–512.
140. Yang Y, Bustani GS, Alawsi T, Altalbawy FMA, Kareem AK, Gupta J, Zhu P, Hjazi A, Alawadi AH, Mustafa YF. The cardioprotective effects of cerium oxide nanoparticles against the poisoning generated by aluminum phosphide pesticide: Controlling oxidative stress and mitochondrial damage. Pesticide Biochemistry and Physiology. 2023;197:105701.
141. Mustafa YF, Mohammed ET, Khalil RR. Synthesis, characterization, and anticoagulant activity of new functionalized biscoumarins. Egyptian Journal of Chemistry. 2021;64(8):4461–8.
142. Najmanova I, Dosedel M, Hrdina R, Anzenbacher P, Filipsky T, Riha M, Mladenka P. Cardiovascular Effects of Coumarins Besides their Antioxidant Activity. Current Topics in Medicinal Chemistry. 2015;15(9):830–49.
143. Dhalla NS, Ostadal P, Tappia PS. Involvement of Oxidative Stress in Mitochondrial Abnormalities During the Development of Heart Disease. Biomedicines. 2025;13(6):1338.
144. Saadati F, Modarresi Chahardehi A, Jamshidi N, Jamshidi N, Ghasemi D. Coumarin: A natural solution for alleviating inflammatory disorders. Current Research in Pharmacology and Drug Discovery. 2024;7:100202.
145. Mergia Terefe E, Catalan Opulencia MJ, Rakhshani A, Ansari MJ, Sergeevna SE, Awadh SA, Polatova DS, Abdulkadhim AH, Mustafa YF, Kzar HH, Al-Gazally ME, Kadhim MM, Taherian G. Roles of CCR10/CCL27–

CCL28 axis in tumour development: mechanisms, diagnostic and therapeutic approaches, and perspectives. Expert Reviews in Molecular Medicine. 2022;24:e37.
146. Margiana R, Hammid AT, Ahmad I, Alsaikhan F, Turki Jalil A, Tursunbaev F, Umar F, Romero Parra RM, Fakri Mustafa Y. Current Progress in Aptasensor for Ultra-Low Level Monitoring of Parkinson's Disease Biomarkers. Critical Reviews in Analytical Chemistry. 2024;54(3):617–32.
147. Fakri Mustafa Y. Coumarins in applied chemical engineering: From natural scaffolds to functional materials. Applied Chemical Engineering. 2025;8(2):5697.
148. Hjazi A, Ghaffar E, Asghar W, Alauldeen Khalaf H, Ikram Ullah M, Mireya Romero-Parra R, Hussien BM, Abdulally Abdulhussien alazbjee A, Singh Bisht Y, Fakri Mustafa Y, Reza Hosseini-Fard S. CDKN2B-AS1 as a novel therapeutic target in cancer: Mechanism and clinical perspective. Biochemical Pharmacology. 2023;213:115627.
149. Abdulaziz NT, Mustafa YF. The Effect of Heat Variable on the Chemical Composition and Bioactivities of a Citrullus lanatus Seed Aqueous Extracts. Journal of Medicinal and Chemical Sciences. 2022;5(7):1166–76.
150. Alam MM, Al-Bahrani HA, Khujaniyozova O, Ali FA, Polatova D, Kholmurodova D, Kuryazov R, Alsalim M, Kuldasheva S, Al-Rashedi NAM, Karamova N, Abomughaid MM, Mustafa YF, Urazbaeva D. Influence of machine learning technology on the development of electrochemical, optical, and image analysis-based methods for biomedical, food, and environmental analysis. Microchemical Journal. 2025;218:115407.
151. Al-Hawary SIS, Saleh EAM, Hadrawi SK, Alkhafaji AT, Tuxtayev J, Sain DK, Juyal A, Alkhayyat MRR, Alsaalamy AH, Mustafa YF. New frontiers and prospects of MXene-based photoelectrochemical sensing system for detection of pollutant in food and environment. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2024;680:132568.
152. Xie J, Wang L, Su X, Rodrigues J. Coumarin-based Fluorescent Probes for Bioimaging: Recent Applications and Developments. Current Organic Chemistry. 2021;25(18):2142–54.
153. Ban AA, Ibrahim BY, Mustafa YF. The Protective Role of Natural Coumarins Derivatives and Anpro Supplement Against Aflatoxin B1 Pollution in the Quails Coturnix Japonica Diet. Mesopotamia Journal of Agriculture. 2023;51(1):1–13.
154. Mustafa YF, Alshaher, Marwa Mohammed Hassan DA, Faisal AF. Synthesis and Medicinal Impacts of Novel 3 , 3 ′ -Bihalocoumarins and Their Precursors , 7-Halocoumarin-3-acetic Acids. Russian Journal of Bioorganic Chemistry. 2025;51(2):802–15.
155. Ramírez-Coronel AA, Alameri AA, Altalbawy F, Sanaan Jabbar H, Lateef Al-Awsi GR, Iswanto AH, Altamimi AS, Shareef Mohsen K, Almulla AF, Mustafa YF. Smartphone-Facilitated Mobile Colorimetric Probes for Rapid Monitoring of Chemical Contaminations in Food: Advances and Outlook. Critical Reviews in Analytical Chemistry. 2024;54(7):2290–308.
156. Sharma A, Verwilst P, Li M, Ma D, Singh N, Yoo J, Kim Y, Yang Y, Zhu JH, Huang H, Hu XL, He XP, Zeng L, James TD, Peng X, Sessler JL, Kim JS. Theranostic Fluorescent Probes. Chemical Reviews. 2024;124(5):2699–804.
157. Abdelbasset WK, Savina SV, Mavaluru D, Shichiyakh RA, Bokov DO, Mustafa YF. Smartphone based aptasensors as intelligent biodevice for food contamination detection in food and soil samples: Recent advances. Talanta. 2023;252:123769.
158. Achmad H, Mazin Al-Hamdani M, Abdul-Jabbar Ali S, Kareem AK, Al-Gazally ME, Alexis Ramírez-Coronel A, Altamimi AS, Abosaooda M, Fakri Mustafa Y, Hayif Jasim Ali S. Recent advances of amino acid-based biosensors for the efficient food and water contamination detection in food samples and environmental resources: A technical and analytical overview towards advanced nanomaterials and biological receptor. Microchemical Journal. 2023;189:108552.
159. Hassan DA, Mustafa YF. The Activity-Enhancing Effect of the 1,3-Dioxolane Ring in Biomedicine. Russian Journal of Bioorganic Chemistry. 2025;51(3):991–1010.
160. Raya I, Widjaja G, HACHEM K, M.N. R, Ahmed AA, M. Kadhim M, Mustafa YF, Mahmood ZH, Aravindhan S. MnCo2O4/Co3O4 Nanocomposites: Microwave-Assisted Synthesis, Characterization and Photocatalytic Performance. Journal of Nanostructures. 2021;11(4):728–35.
161. Jebir MR, Mustafa YF. Kidney stones: natural remedies and lifestyle modifications to alleviate their burden. International Urology and Nephrology. 2024;56(3):1025–33.
162. Ismael RN, Mustafa YF, Al-Qazaz HK. Cancer-curative potential of novel coumarins from watermelon princess : A scenario of their isolation and activity. Eurasian Chemical Communications. 2022;4(7):657–72.
163. Hammoodi SH, Ismael SS, Mustafa YF. Mutual prodrugs for colon targeting: A review. Eurasian Chemical Communications. 2022;4(12):1251–65.
164. Ismael SS, Waheed NAM, Kasim SM, Mustafa YF. Novel Coumarin-Indole Hybrids as Cytotoxic Candidates: Synthesis and Antiproliferative Activity. Pharmacognosy Journal. 2023;15(6):1105–11.
165. Mustafa YF. When the gut Speaks: The hidden toll of irritable bowel syndrome on body and mind. Gastroenterology & Endoscopy. 2025;3(3):135–51.

166. Ebrahimipour SY, Mirzaei M, Zamani K, Mohamadi M, Ghaffarian-Bahraman A, Ramezanpour S. Characterization and In-vitro release of coumarin from folic acid-conjugated mesoporous silica for targeted cancer therapy. Journal of Molecular Structure. 2025;1330:141502.
167. Mustafa YF. Role of Fruit-Derived Antioxidants in Fighting Cancer: A Narrative Review. Indian Journal of Clinical Biochemistry. 2025;40(4):522–39.
168. Hassan DA, Mustafa YF. Novel 1,3-dioxolane–coumarin hybrids: From synthesis to pharmacological In Vitro-In Silico profiling. Applied Chemical Engineering. 2025;8(1):5651.
169. Mustafa YF, Oglah MK, Bashir MK, Mohammed ET, Khalil RR. Mutual prodrug of 5-ethynyluracil and 5-fluorouracil: Synthesis and pharmacokinetic profile. Clinical Schizophrenia and Related Psychoses. 2021;15(5):1–6.
170. Alshaher MM, Mustafa YF. Synthesis of Dioxane-fused Coumarins as a new class of biosafe multifunctional therapeutic candidates : A journey from In Vitro to In Silico prediction. Applied Catalysis B: Environmental. 2025;8(1):5652.
171. Mustafa YF, Mohammed NA alwahab. A promising oral 5-fluorouracil prodrug for lung tumor: Synthesis, characterization and release. Biochemical and Cellular Archives. 2021;21(Supp 1):1991–9.
172. Li J, Wang Q, Xia G, Adilijiang N, Li Y, Hou Z, Fan Z, Li J. Recent Advances in Targeted Drug Delivery Strategy for Enhancing Oncotherapy. Pharmaceutics. 2023;15(9):2233.
173. Mustafa YF, Abdulaziz NT. Hymecromone and its products as cytotoxic candidates for brain cancer : A brief review. NeuroQuantology. 2021;19(7):175–86.
174. Son A, Park J, Kim W, Lee W, Yoon Y, Ji J, Kim H. Integrating Computational Design and Experimental Approaches for Next-Generation Biologics. Biomolecules. 2024;14(9):1073.
175. Jasim MHM, Mustafa YF. Synthesis of Acetaminophen-Based Coumarins as Selective COX-2 Inhibitors: An in vitro-in silico Study. Chemistry & Biodiversity. 2024;21(10):e202401309.
176. Li J, Zhao T, Yang Q, Du S, Xu L. A review of quantitative structure-activity relationship: The development and current status of data sets, molecular descriptors and mathematical models. Chemometrics and Intelligent Laboratory Systems. 2025;256:105278.
177. Zeki NM, Mustafa YF. Harnessing Artificial Intelligence to Discover the Therapeutic Potential of Natural Coumarins: A Review Study. Russian Journal of Bioorganic Chemistry. 2025;51(4):1432–52.
178. Mehta S, Pathak SR. Insilico Drug Design And Molecular Docking Studies Of Novel Coumarin Derivatives As Anti-Cancer Agents. Asian Journal of Pharmaceutical and Clinical Research. 2017;10(4):335.
179. Kasmi R, Hadaji E, Chedadi O, El Aissouq A, Bouachrine M, Ouammou A. 2D-QSAR and docking study of a series of coumarin derivatives as inhibitors of CDK (anticancer activity) with an application of the molecular docking method. Heliyon. 2020;6(8):e04514.
180. Mazin Zeki N, M.Z. Othman K, Fakri Mustafa Y. Computational Chemistry: A game-changer in the drug discovery field. Applied Chemical Engineering. 2025;8(1):ACE-5601.
181. Faisal AF, Mustafa YF. The role of coumarin scaffold in the chemical engineering of bioactive molecules: A narrative review. Applied Chemical Engineering. 2025;8(1):ACE-5595.
182. Mustafa YF, Bashir MK, Oglah MK. Synthesis, antioxidant and antitumor activities of new coumarins grafted to 5-fluorouracil. Caspian Journal of Environmental Sciences. 2022;20(2):359–65.
183. Al Abdeen SHZ, Mustafa YF, Mutlag SH. Synthesis of disubstituted anisolodipyronederived ester compounds: The search for new bioactive candidates. Eurasian Chemical Communications. 2022;4(11):1171–83.
184. Ahmed BA, Mustafa YF, Ibrahim BY. Isolation and characterization of furanocoumarins from Golden Delicious apple seeds. Journal of Medicinal and Chemical Sciences. 2022;5(4):537–45.
185. Patil VM, Gupta SP, Masand N, Balasubramanian K. Experimental and computational models to understand protein-ligand, metal-ligand and metal-DNA interactions pertinent to targeted cancer and other therapies. European Journal of Medicinal Chemistry Reports. 2024;10:100133.
186. Mustafa YF. Coumarins as natural aphrodisiacs: Mechanistic insights and future perspectives in male sexual health. Fitoterapia. 2025;187:106928.
187. Ansari MJ, Jasim SA, Abed AM, Altimari US, Yasin G, Suksatan W, Oudaha KH, Kadhim MM, Jabbar AH, Mustafa YF. Double chelation of Iron through dimer formation of favipiravir: Density functional theory analysis. Main Group Chemistry. 2022;21(3):875–83.
188. Waheed SA, Mustafa YF. The in vitro effects of new albocarbon-based coumarins on blood glucose-controlling enzymes. Journal of Medicinal and Chemical Sciences. 2022;5(6):954–67.
189. Mustafa YF, Al-Shakarchi W. The psychotropic potential of coumarins: Mechanisms, efficacy, and future prospects. Environment and Social Psychology. 2025;10(3):3534.
190. Zhu L, Zhang L, Yang Z, Pu M, Lei M. A theoretical study of the hydroboration of α,β-unsaturated carbonyl compounds catalyzed by a metal-free complex and subsequent C–C coupling with acetonitrile. New Journal of Chemistry. 2021;45(31):14134–40.
191. Abdulaziz NT, Mustafa YF. Anticancer properties of hymecromone-derived compounds: A review. International Journal of Pharmaceutical Research. 2021;13(1):2163–74.

192. Mustafa YF, Abdulaziz NT. Anticancer potential of hymecromone-based compounds: A review. Biochemical and Cellular Archives. 2021;21(2):4151–61.
193. Al-Shakarchi W, Saber Y, Merkhan MM, Mustafa YF. Sub Chronic Toxicity Study of Coumacines. Pharmacognosy Journal. 2023;15(1):160–4.
194. Al-Shakarchi W, Saber Y, Merkhan MM, Mustafa YF. Acute toxicity of coumacines: An in vivo study. Georgian medical news. 2023;(338):126–31.
195. Younis MA, Hamid OA, Dhaher R, Saber Y, Al-shakarchi W, Merkhan MM, Mustafa YF. Characterization of the renal safety profiles of coumacines. Pharmakeftiki. 2023;35(4):57–63.
196. Maashi MS, Al-Mualm M, Al-Awsi GRL, Opulencia MJC, Al-Gazally ME, Abdullaev B, Abdelbasset WK, Ansari MJ, Jalil AT, Alsaikhan F, Shalaby MN, Mustafa YF. Apigenin alleviates resistance to doxorubicin in breast cancer cells by acting on the JAK/STAT signaling pathway. Molecular Biology Reports. 2022;49:8777–84.
197. Anywar G, Muhumuza E. Bioactivity and toxicity of coumarins from African medicinal plants. Frontiers in Pharmacology. 2024;14:1231006.
198. Abdelbasset WK, Elkholi SM, Ismail KA, AL-Ghamdi HS, Mironov S, Ridha HSH, Maashi MS, Thangavelu L, Mahmudiono T, Mustafa YF. Mequinol-loaded carboxymethyl cellulose/chitosan electrospun wound dressing as a potential candidate to treat diabetic wounds. Cellulose. 2022;29(14):7863–81.
199. Kaplan BLF, Hoberman AM, Slikker W, Smith MA, Corsini E, Knudsen TB, Marty MS, Sobrian SK, Fitzpatrick SC, Ratner MH, Mendrick DL. Protecting Human and Animal Health: The Road from Animal Models to New Approach Methods. Pharmacological Reviews. 2024;76(2):251–66.
200. Flores-Morales V, Villasana-Ruíz AP, Garza-Veloz I, González-Delgado S, Martinez-Fierro ML. Therapeutic Effects of Coumarins with Different Substitution Patterns. Molecules. 2023;28(5):2413.