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REVIEW ARTICLE

Integrating chemical engineering approaches in the biomedical utilization of coumarin derivatives

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ABSTRACT

Background: Coumarin derivatives, characterized by their benzopyrone core, represent a diverse class of natural and synthetic compounds with significant biomedical potential, including antimicrobial, antioxidant, and anticancer activities. Integrating chemical engineering principles into their design, synthesis, and scale-up offers opportunities to optimize production, enhance functionality, and support sustainable biomedical applications. **Methods:** This review synthesizes literature on the biomedical utilization of coumarin derivatives from a chemical engineering perspective. Emphasis is placed on traditional and green synthetic methodologies, characterization techniques (UV–Vis, FT-IR, NMR, MS, GC), and process optimization strategies. Reaction kinetics, process design, and scale-up approaches are discussed alongside their influence on pharmacological performance. **Results:** Coumarin derivatives have been effectively synthesized through both classical methods (e.g., Pechmann, Knoevenagel, Perkin reactions) and eco-friendly routes utilizing microwave assistance, solid-supported catalysts, and ionic liquids. Structural characterization confirmed their identity, purity, and functional group modifications. Pharmacological evaluations demonstrated broad biological activity, including potent antimicrobial effects against Gram-positive and Gram-negative bacteria, strong antioxidant properties via free-radical scavenging, and notable anticancer activity through apoptosis induction. The application of chemical engineering principles improved yields, reduced hazardous waste, and facilitated pilot-to-industrial scale transitions while maintaining product quality. **Conclusion:** The synergy between chemical engineering and medicinal chemistry provides a framework for the sustainable production and biomedical advancement of coumarin derivatives. By aligning synthetic design with reaction kinetics, green chemistry principles, and regulatory safety standards, coumarin-based therapeutics can be developed more efficiently. This interdisciplinary approach holds promise for expanding their role in next-generation drug delivery systems and targeted therapies.

Keywords: coumarins; sustainable synthesis; process optimization; chemical engineering; scale-up technique

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1. Introduction

Coumarins constitute a broad and chemically diverse class of naturally occurring compounds, unified by a characteristic benzo-α-pyrone core. This structural framework is formed through lactonization and α-pyrone ring closure of hydroxylated 2-cinnamic acid derivatives[1]. Within this family, multiple structural variants exist—including isocoumarins, furanocoumarins, pyranocoumarins, biscoumarins, and their homologs—each retaining the core skeleton yet exhibiting distinct physicochemical properties[2]. Extensive research has revealed that coumarin derivatives possess a wide range of pharmacological activities, notably antimicrobial[3], antioxidant[4], and anticancer[5] effects. These properties underpin their growing importance as promising candidates in drug delivery and therapeutic development[6].

Both naturally derived and synthetically engineered coumarins have been the focus of considerable scientific attention, with parallel efforts directed at expanding their utility through chemical-engineering-driven approaches, particularly in the biomedical domain[7]. Drug development—central to improving human health and longevity—benefits greatly from chemical engineering, which integrates disciplines such as reaction engineering, process design, and reactor operation to translate laboratory-scale synthesis into efficient industrial processes[8]. Optimization of reaction yields, guided by kinetic studies, plays a crucial role in the commercial feasibility of coumarin production[9].

The synthesis of coumarin derivatives employs diverse strategies, ranging from conventional chemical methods to modern, eco-friendly approaches such as photo-induced cyclization, hydrothermal processing, and microwave-assisted synthesis[10]. To fully realize their biomedical potential, these compounds require comprehensive characterization, in-depth evaluation of their pharmacological profiles, and the strategic identification of applications that bridge medicinal chemistry and chemical engineering principles.

2. Chemical engineering principles in biomedical applications

The biomedical utilization of coumarins is deeply rooted in the fundamental principles of chemical engineering, which bridge molecular science with practical, large-scale applications[11]. At its core, chemical engineering involves the design, optimization, and scaling of processes that transform raw materials into valuable products—principles that are essential when translating coumarin research from laboratory synthesis to clinical use[12]. In coumarin-based drug development, reaction engineering plays a pivotal role in designing synthetic pathways that maximize yield, purity, and cost-effectiveness while minimizing environmental impact. Controlled reaction kinetics, catalysis, and thermodynamic optimization enable the selective production of coumarin derivatives with targeted pharmacological activities[13]. Additionally, process intensification techniques—such as continuous-flow synthesis—offer superior scalability and reproducibility, making them ideal for producing coumarins with strict quality standards required in biomedical applications[14].

Separation and purification approach, another cornerstone of chemical engineering, ensures that bioactive coumarin compounds are isolated in their pure form without compromising structural integrity[15]. Advanced purification strategies, including chromatographic and membrane-based methods, are often employed to remove reaction by-products and residual solvents. These processes directly influence the safety and efficacy of coumarin-based formulations in therapeutic and diagnostic applications[16]. Transport phenomena—covering mass, heat, and momentum transfer—further guide the formulation of coumarin-containing biomedical products. Understanding how coumarins diffuse across membranes, dissolve in different media, or interact with nanocarriers informs the design of delivery systems that enhance bioavailability and targeted action[17]. For instance, encapsulation in polymeric nanoparticles or lipid-based vesicles can be engineered to modulate release kinetics, protect coumarins from premature degradation, and improve their accumulation at diseased sites[18].

From a systems engineering perspective, the integration of computational modeling and process control ensures that coumarin production adheres to Good Manufacturing Practices[19]. Process simulations and digital twins enable researchers to predict reaction behavior, optimize process parameters, and maintain product quality at industrial scale. Such approaches not only accelerate the development timeline but also align with regulatory requirements for biomedical products[20]. Ultimately, the successful biomedical application of coumarins depends on the seamless interplay between chemical engineering principles and pharmacological innovation. By leveraging process design, reaction optimization, transport analysis, and quality control, researchers can transform coumarins from promising bioactive molecules into safe, effective, and commercially viable therapeutic agents[21].

3. Synthesis of coumarin derivatives

Chemical engineering perspectives on the biomedical applications of coumarin derivatives extend far beyond the simple collation of literature on their chemistry and pharmacology. This field encompasses a range of engineering-driven approaches, such as analyzing reaction kinetics for coumarin synthesis, optimizing process parameters for large-scale pharmaceutical manufacturing, and applying process engineering principles to enhance yield, purity, and sustainability[22]. While many recent reviews on coumarin derivatives emphasize their chemical structures, pharmacological potential, and biological activities[23–25], integrating chemical engineering concepts allows for a more holistic understanding of their biomedical relevance. Coumarins are naturally occurring benzopyranone derivatives, widely used not only for their therapeutic potential but also in cosmetics, where they contribute to skin- and hair-lightening effects. Growing environmental concerns have shifted research efforts toward the development of green, eco-friendly synthesis strategies[26].

Modern characterization techniques—such as UV–Visible and fluorescence spectroscopy, FT-IR, ^{1}H and ^{13}C NMR spectroscopy, and GC–MS—play a crucial role in confirming the structural integrity and purity of synthesized coumarin derivatives[27]. These compounds are frequently evaluated for antimicrobial[28], antioxidant[29], and anticancer[30] properties, with promising implications for applications ranging from drug delivery systems to antibacterial agents, anticancer therapeutics, anti-HIV drugs, anticoagulants, and antioxidant supplements[31]. Traditionally, coumarins have been synthesized using classical organic transformations, including the Pechmann, Perkin, Knoevenagel, Reimer–Tiemann, and Mannich reactions. These methods often rely on acid- or base-catalyzed condensations between phenols and β-ketoesters under varying conditions[32]. In recent years, advancements in green chemistry have introduced more sustainable synthetic approaches, such as solid-supported catalysts, ionic liquids, microwave-assisted organic synthesis, and enzyme-mediated reactions, which reduce energy consumption, minimize waste, and align with environmentally responsible manufacturing practices[33].

Traditional synthesis methods

Coumarins belong to the benzopyrone family, specifically to the chromone subgroup (1,2-benzopyrone), characterized by a fused benzene and α-pyrone ring with the molecular formula $C_9H_6O_2$. This simple yet versatile scaffold forms the basis for a wide range of derivatives with distinct chemical architectures and significant pharmacological potential. Over the years, extensive research has demonstrated that coumarin derivatives exhibit diverse bioactivities, including antimicrobial[34], antioxidant[35], and anticancer[36] properties, making them valuable assets in modern medical science.

Owing to their broad therapeutic relevance, coumarin derivatives have found widespread applications in biomedical research and healthcare. To date, roughly 150 naturally occurring coumarin-related compounds have been identified with notable free-radical scavenging capabilities. Synthetic approaches to coumarin derivatives remain essential, not only for expanding structural diversity but also for reducing undesirable side effects[37]. Strategic substitution at different positions of the benzene ring plays a pivotal role in enhancing biological performance and generating compounds with industrial significance. Incorporating heterocyclic moieties into the coumarin framework has further broadened their pharmacological repertoire, yielding molecules with antimicrobial[38], antipsychotic[39], anti-obesity[40], anticancer[41], anticoagulant[42], anti-inflammatory[43], anticonvulsant[44], analgesic[45], and other therapeutic activities.

Traditionally, coumarin derivatives have been synthesized using classical organic reactions such as the Pechmann, Perkin, and Knoevenagel condensations. While these methods are effective, they often rely on hazardous solvents and toxic reagents, raising concerns over environmental impact and sustainability[46]. As a result, there is increasing interest in greener, more sustainable synthetic strategies for coumarin derivatives that align with modern principles of green chemistry.

Green chemistry approaches

The growing demand for environmentally sustainable practices in chemical synthesis has spurred the adoption of green chemistry principles for coumarin production. Traditional synthetic routes, while effective, often rely on hazardous solvents, energy-intensive conditions, and toxic reagents that pose significant environmental and health concerns[47]. In contrast, green methodologies emphasize the use of safer solvents, renewable resources, milder reaction conditions, and energy-efficient processes to minimize waste generation and ecological impact[48]. One of the most widely explored eco-friendly routes for coumarin synthesis, as illustrated in **Figure 1**, is solvent-free or solvent-minimized reactions, which eliminate the hazards associated with volatile organic compounds. In such systems, reactants are often activated through mechanical mixing, ultrasound irradiation, or microwave heating, significantly reducing reaction times and improving yields[49]. Microwave-assisted Pechmann condensation, for example, allows the rapid cyclization of phenols with β-ketoesters under acid catalysis without the need for harmful solvents, producing coumarins in high purity with minimal by-products[50].

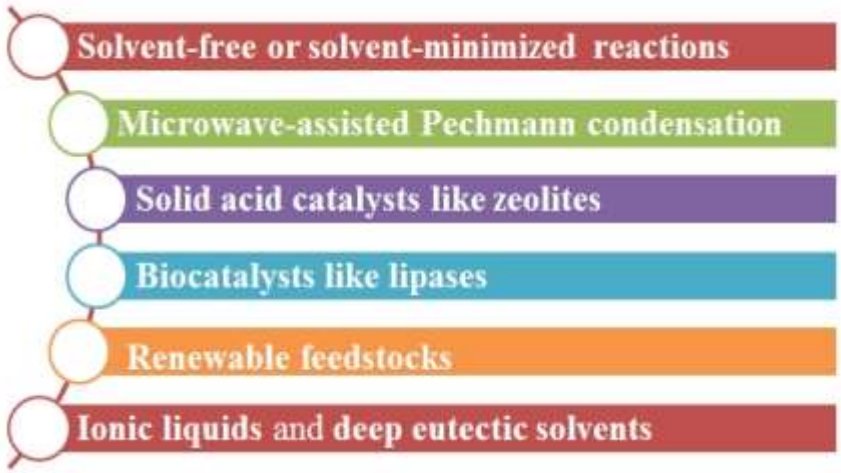


Figure 1. Investigated green chemistry synthetic approaches for coumarins.

Another promising strategy involves the use of biocatalysts, such as lipases and other enzymes, to mediate key bond-forming steps under mild, aqueous conditions. These biotransformations operate at ambient temperature and pressure, reducing both energy consumption and the formation of toxic residues[51]. Similarly, solid acid catalysts like zeolites, clays, and heteropolyacids offer recyclable, non-corrosive alternatives to traditional mineral acids, enabling cleaner and more sustainable coumarin synthesis[52]. Ionic liquids and deep eutectic solvents have also emerged as versatile green media for coumarin synthesis. These designer solvents combine low volatility with high thermal stability, providing tunable polarity for optimized reaction efficiency while reducing environmental hazards[53]. In many cases, they also serve dual roles as both solvents and catalysts, further simplifying reaction work-up[54].

The integration of renewable feedstocks, such as plant-derived phenolic compounds and bio-based β-ketoesters, aligns with the circular economy model and ensures that coumarin synthesis can be achieved with minimal reliance on petroleum-derived chemicals[55]. Coupling these renewable precursors with low-energy processes—such as visible-light photocatalysis—further enhances sustainability while opening avenues for novel functionalized coumarins with high bioactivity[56]. Ultimately, green chemistry approaches not only reduce the environmental footprint of coumarin production but also improve cost-effectiveness, reaction selectivity, and scalability. These innovations position coumarins as exemplary molecules in the shift toward more sustainable chemical manufacturing, balancing industrial demand with ecological responsibility[57].

4. Characterization techniques for coumarin derivatives

Structural analysis is a fundamental step in the comprehensive characterization of any chemical compound, providing critical insight into its identity, purity, and functional properties. In the case of coumarin derivatives, this process commonly employs a combination of analytical techniques, including UV–visible and Fourier-transform infrared (FT-IR) spectroscopy, gas chromatography (GC), and mass spectrometry (MS). These methods allow researchers to determine the electronic, vibrational, and molecular fragmentation patterns of the compounds, thereby confirming their structural integrity[58].

For example, Molnar et al. employed a range of assays—such as the pyrogallol and phenanthroline methods, 2,2-diphenyl-1-picrylhydrazyl radical scavenging test, agar diffusion, microdilution, and MTT cytotoxicity assays—to evaluate the physicochemical and biological characteristics of synthesized coumarins[59]. Similarly, Avdović et al. prepared a series of coumarin derivatives and verified their molecular structures through multiple spectroscopic analyses[60]. Kumar et al. investigated the influence of sugar reduction on the green synthesis of coumarin derivatives, particularly focusing on their nonlinear optical properties[61]. In another study, Abdel-Kader et al. reported the synthesis of a coumarin-based Schiff base and its Cu(II) complex, characterizing these materials via elemental microanalysis, FT-IR spectroscopy, mass spectrometry, and ^{1}H NMR spectroscopy[62]. Finally, Karcz et al. relied extensively on spectroscopic techniques to elucidate the structural features of coumarin-derived compounds[63].

Spectroscopic methods

Given the structural complexity and substitutional diversity of coumarins, the use of multiple, complementary spectroscopic methods, as recorded in **Table 1**, ensures comprehensive characterization and facilitates structure–activity relationship studies. Ultraviolet–visible (UV–Vis) spectroscopy is often the first step in coumarin analysis due to the strong π–π* transitions of the benzopyrone chromophore. Coumarin derivatives typically exhibit characteristic absorption bands in the near-UV region, with shifts in wavelength and intensity reflecting variations in substituent type and position. These spectral changes can be used to monitor reaction progress, assess purity, and study solvent effects or molecular interactions, particularly in the context of photophysical applications[64].

Separately, fluorescence spectroscopy provides additional sensitivity in characterizing coumarins, as many derivatives display intense fluorescence emission resulting from their rigid conjugated structure. Fluorescence measurements not only confirm the presence of the coumarin moiety but also offer information on quantum yields, emission maxima, and potential quenching or enhancement effects from specific substitutions. This property is especially important in the design of coumarin-based probes, sensors, and imaging agents[65]. Also, Fourier-Transform Infrared (FT-IR) spectroscopy serves to identify functional groups within coumarin derivatives. The carbonyl stretching vibration of the lactone ring, usually observed in the 1700–1725 cm^{-1} region, is a diagnostic feature, while aromatic C–H stretches, C=C aromatic stretches, and characteristic peaks from substituent groups provide additional structural confirmation. Comparative analysis of FT-IR spectra before and after synthetic modification can validate successful functionalization[66].

On the other hand, Nuclear Magnetic Resonance (NMR) spectroscopy—both ^{1}H and ^{13}C NMR—remains indispensable for precise structural elucidation. ^{1}H NMR reveals the chemical shifts, multiplicities, and coupling constants of aromatic and aliphatic protons, enabling assignment of proton environments in the coumarin core and attached substituents. ^{13}C NMR further clarifies the electronic environment of carbon atoms, with the lactone carbonyl carbon typically resonating downfield. Advanced 2D NMR experiments, such as COSY, HSQC, and HMBC, are invaluable for mapping atom connectivity in complex derivatives[67].

Finally, Mass spectrometry (MS) complements spectroscopic data by confirming molecular weight and providing fragmentation patterns indicative of structural motifs. Coupling MS with chromatographic

separation (LC–MS) allows rapid identification of reaction products and impurities, making it particularly useful in multi-step synthetic workflows[68]. Together, these spectroscopic techniques offer a comprehensive toolkit for the reliable characterization of coumarin derivatives. Their combined application not only ensures structural verification but also supports the rational design of derivatives with tailored physicochemical and pharmacological properties[69].

Table 1. Spectroscopic methods for characterizing coumarin derivatives.

Spectroscopic method	Key parameters	Information provided	Typical observations in coumarin derivatives	Ref.
UV–Vis	Absorption maxima (λ_{max}) and molar absorptivity	Electronic transitions, conjugation effects, and solvent interactions	Strong π–π* transitions in near-UV (~320–380 nm) and shifts with substituents	[70]
Fluorescence spectroscopy	Emission maxima, quantum yield, and fluorescence lifetime	Photophysical properties and probe/sensor potential	Intense fluorescence and emission shifts depending on substitution as well as polarity	[71]
FT-IR spectroscopy	Wavenumber (cm^{-1}) of characteristic vibrations	Functional group identification	Lactone C=O stretch (~1700–1725 cm^{-1}), aromatic C–H (~3000–3100 cm^{-1}), and C=C stretches	[72]
^{1}H NMR spectroscopy	Chemical shifts (δ, ppm), multiplicities, and coupling constants	Proton environment and connectivity	Aromatic protons (δ 6–8 ppm), lactone ring protons, and substituent-specific signals	[73]
^{13}C NMR spectroscopy	Carbon chemical shifts (δ, ppm)	Carbon framework mapping	Carbonyl carbon (~160–165 ppm), aromatic carbons, and substituent carbons	[74]
2D NMR (COSY, HSQC, HMBC)	Proton–proton and proton–carbon correlations	Detailed structural elucidation	Confirms connectivity between core and substituents	[75]
MS	m/z values to define fragmentation pattern	Molecular weight, molecular formula, and structural fragments	Molecular ion peak matching theoretical molecular weight, and characteristic fragmentation of lactone ring	[76]
LC–MS	Retention time coupled with m/z values	Compound identification in mixtures	Rapid verification of purity and product identity	[77]

Chromatographic methods

Chromatographic methods, as reported in **Table 2**, represent indispensable tools for the qualitative and quantitative characterization of coumarin derivatives, enabling precise separation, identification, and purity assessment. Due to the structural diversity of coumarins and their derivatives, chromatographic profiling is essential for confirming synthetic outcomes, detecting impurities, and evaluating the stability of pharmaceutical formulations[78]. The choice of chromatographic technique is influenced by the physicochemical properties of the compound, including polarity, molecular weight, and the presence of specific functional groups[79].

High-Performance Liquid Chromatography (HPLC) is the most widely employed method for coumarin analysis, offering high resolution, reproducibility, and adaptability to a wide range of coumarin-based compounds. Reverse-phase HPLC, typically using C18 columns, is particularly effective due to the moderate hydrophobicity of the benzopyrone core[80]. Gradient elution with aqueous-organic mobile phases—often involving acetonitrile or methanol with suitable buffers—allows efficient separation of coumarin derivatives differing in substitution pattern and polarity. Coupling HPLC with UV–Vis detection exploits the strong absorbance of the coumarin chromophore, typically around 320–350 nm, while LC–MS integration enables detailed molecular mass confirmation and structural elucidation[81].

Thin-Layer Chromatography (TLC) remains a valuable, cost-effective, and rapid technique for preliminary analysis during coumarin synthesis. Using silica gel or alumina plates, TLC enables quick

monitoring of reaction progress, identification of major products, and estimation of compound purity. Visualization is straightforward, as coumarins exhibit natural fluorescence under UV light, facilitating rapid detection without the need for additional reagents[82]. Gas Chromatography (GC) is suitable for volatile coumarin derivatives or their derivatized forms. While native coumarins may exhibit limited volatility, chemical derivatization—such as silylation—can enhance their GC compatibility. Coupling GC with mass spectrometry (GC–MS) provides sensitive and accurate molecular identification, aiding in impurity profiling and degradation studies[83].

Advanced multidimensional chromatography, such as HPLC–HPLC or LC–GC coupling, has also been applied to complex natural extracts containing multiple coumarins. These systems improve separation efficiency and provide deeper insight into compositional complexity, especially when characterizing bioactive compounds from plant or marine sources[84]. In essence, chromatographic techniques form the analytical backbone for coumarin characterization, supporting every stage from synthetic route development to final quality control[85]. Their adaptability, combined with detection systems such as UV, fluorescence, and mass spectrometry, ensures comprehensive analysis tailored to the unique properties of each coumarin derivative[86].

Table 2. Chromatographic techniques for the characterization of coumarin derivatives.

Technique	Principle	Key advantages	Limitations	Typical applications for coumarins	Ref.
HPLC	Separation based on differential interaction with stationary phase (often C18) and mobile phase composition	High resolution, reproducibility, adaptable to polar and nonpolar coumarins, and compatible with various detectors (UV, fluorescence, MS)	Requires expensive equipment and longer analysis time compared to TLC	Quantitative purity analysis, identification of synthetic products, and pharmacokinetic studies	[87]
Reverse-Phase HPLC	Nonpolar stationary phase with polar mobile phase; retention inversely related to polarity	Excellent for moderately hydrophobic coumarins and strong UV absorbance detection	Limited for highly volatile derivatives	Separation of coumarins differing in substitution pattern and lipophilicity	[88]
TLC	Separation on a thin stationary layer (silica gel/alumina) with solvent migration	Fast, inexpensive, minimal sample preparation, and visualized under UV	Low resolution, qualitative or semi-quantitative only	Monitoring synthesis, reaction progress, and quick purity checks	[89]
GC	Separation of volatile compounds in gas phase through capillary columns	High resolution for volatile derivatives, rapid analysis, and compatible with MS	Coumarins often require derivatization, limited for thermally labile compounds	Analysis of volatile synthetic coumarin derivatives and impurity profiling	[90]
LC–MS	HPLC coupled with mass spectrometry for molecular mass and structure determination	Highly specific, sensitive, provides structural data	High cost, requires expertise	Structural elucidation, impurity identification, and metabolite profiling	[91]
GC–MS	GC coupled with MS for volatile compounds	Powerful for complex mixtures with precise molecular identification	Requires volatility or derivatization	Detection of volatile degradation products and environmental coumarin analysis	[92]
Multidimensional	Sequential use of two chromatographic	High peak capacity, improved resolution	More complex setup with higher	Comprehensive profiling of	[93]

Technique	Principle	Key advantages	Limitations	Typical applications for coumarins	Ref.
chromatography	modes	of complex mixtures	operational cost	plant/marine extracts rich in coumarins	

Table 2. (*Continued*)

5. Pharmacological properties of coumarin derivatives

Chemical engineering plays a pivotal role in the design, optimization, and scaling of processes for manufacturing, transforming, and transporting materials. By integrating principles of chemistry, physics, mathematics, and economics, it enables the development of greener and more efficient synthetic protocols for coumarins[94]. The optimization of synthetic routes is intrinsically linked to the enhancement of pharmacological properties, illustrating a clear interdependence between process design and biomedical potential[95].

Importantly, the evolution of coumarin-based therapeutics is not confined to the domain of organic chemistry; rather, it reflects the interdisciplinary synergy between chemical engineering and biomedicine. Process design strategies, such as reaction kinetics analysis and process control methodologies, are central to improving yield, purity, and sustainability in coumarin synthesis[96]. In this context, coumarin derivatives serve as an illustrative model for demonstrating how chemical engineering innovations can drive biomedical advancements. The relationship between catalytic reaction kinetics and derivative formation exemplifies the crucial link between efficient production and the realization of their therapeutic potential[97].

Antimicrobial activity

Coumarin derivatives have attracted considerable attention as promising scaffolds in the development of novel antimicrobial agents. Their core benzopyrone structure, coupled with the ease of functional modification, allows for the synthesis of a wide variety of analogues with enhanced pharmacological properties. Many naturally occurring and synthetically engineered coumarins exhibit potent activity against bacterial[98], fungal[99], viral[100], and even mycobacterial[101] pathogens through various mechanisms, as shown in **Figure 2**. This versatility stems from their ability to interact with diverse molecular targets, disrupt critical microbial metabolic processes, and inhibit essential enzymes, leading to impaired growth or cell death[102].

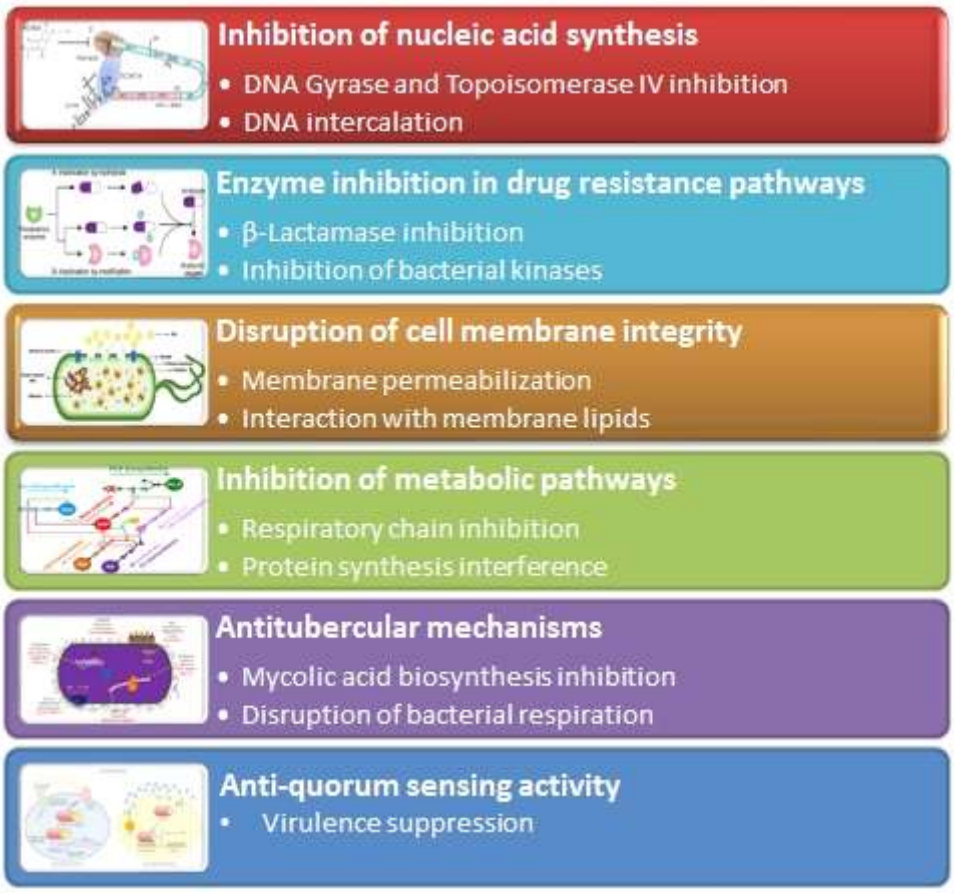


Figure 2. Mechanisms and sub-mechanisms related to the antimicrobial activity of coumarin derivatives.

Numerous coumarin-based compounds display significant antibacterial activity against both Gram-positive and Gram-negative bacteria. They have shown inhibitory effects on clinically relevant strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*. Their mechanisms of action include inhibition of bacterial DNA gyrase and topoisomerase IV, disruption of cell wall biosynthesis, and interference with quorum sensing pathways, which collectively impair bacterial replication and virulence[103–105]. Importantly, certain coumarin derivatives have demonstrated activity against multidrug-resistant strains, highlighting their potential in addressing the global challenge of antibiotic resistance[106].

Beyond antibacterial effects, coumarin derivatives also exhibit potent antifungal properties, targeting pathogens such as *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. These compounds can disrupt fungal cell membrane integrity, inhibit ergosterol biosynthesis, and interfere with oxidative stress regulation, ultimately impairing fungal viability[107]. Additionally, several coumarin analogues have shown antitubercular activity by inhibiting *Mycobacterium tuberculosis* growth, potentially through the disruption of mycolic acid synthesis or interference with bacterial respiration. Such findings position coumarins as valuable leads for the development of therapeutics against tuberculosis, especially in drug-resistant cases[108].

One of the remarkable features of coumarin derivatives is their broad-spectrum antimicrobial potential, which often extends beyond a single pathogen type. Certain structural modifications yield compounds with dual antibacterial and antifungal properties, reducing the need for combination therapy[109]. This multifunctionality is particularly advantageous in treating mixed infections or in environments where rapid microbial adaptation can lead to resistance[110]. Coumarin-based drug design continues to evolve, with ongoing research focused on optimizing their potency, selectivity, pharmacokinetics, and safety profiles, ensuring their relevance in future antimicrobial therapy.

Antioxidant properties

Coumarin derivatives have attracted significant scientific attention for their pronounced antioxidant potential, which plays a vital role in counteracting oxidative stress–related disorders[111]. The antioxidant mechanisms, as displayed in **Figure 3**, of these molecules are primarily attributed to their unique benzopyrone scaffold, which allows them to scavenge reactive oxygen species and reactive nitrogen species effectively. By donating electrons or hydrogen atoms, coumarin derivatives can neutralize free radicals, thus preventing the initiation and propagation of lipid peroxidation and protecting essential biomolecules such as DNA, proteins, and lipids from oxidative damage[112]. Structural modifications, particularly the introduction of hydroxyl, methoxy, or prenyl groups at specific positions of the coumarin nucleus, have been shown to enhance their radical-scavenging efficiency and overall antioxidant capacity[113].

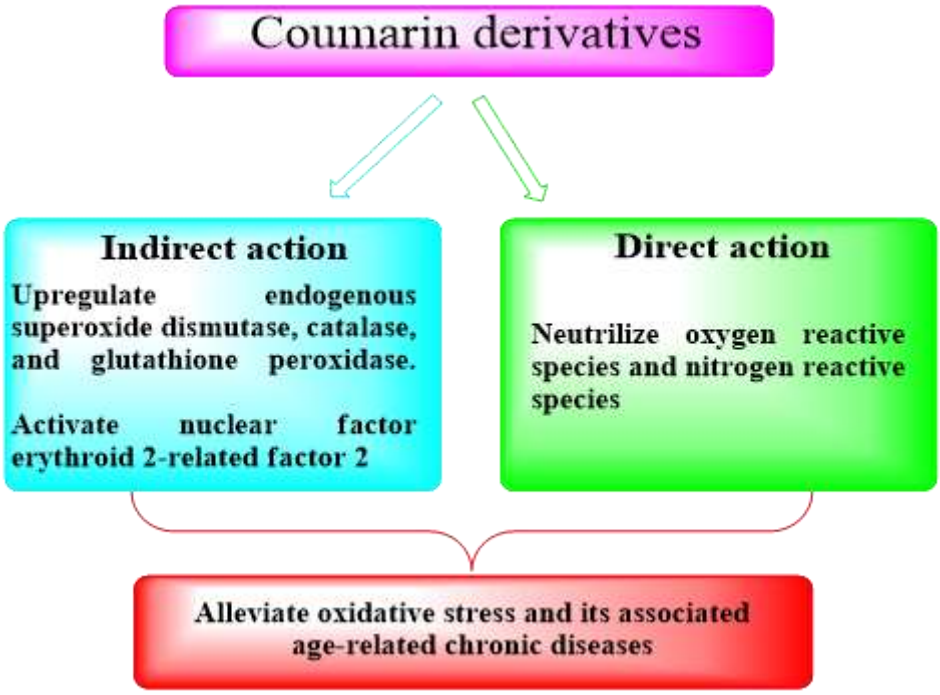


Figure 3. The antioxidant mechanisms of the coumarin derivatives.

In addition to their direct free radical–scavenging ability, coumarin derivatives exhibit indirect antioxidant effects by modulating cellular defense mechanisms. Several derivatives have been reported to upregulate endogenous antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, thereby reinforcing the cellular antioxidant network[114]. They may also activate key transcription factors such as nuclear factor erythroid 2–related factor 2, which governs the expression of antioxidant response elements-dependent genes[115]. This dual action—direct neutralization of radicals and activation of intrinsic defense pathways—makes coumarin derivatives promising candidates for preventing and managing diseases linked to oxidative stress[116], including neurodegenerative disorders[117], cardiovascular diseases[118], diabetes[119], and certain cancers[120].

Furthermore, studies have demonstrated that the antioxidant activity of coumarin derivatives is influenced by their physicochemical properties, such as lipophilicity and electronic distribution, which dictate their interaction with radical species and biological membranes[121]. The conjugated π-system within the coumarin structure facilitates electron delocalization, stabilizing the resultant radical forms and improving antioxidant stability[122]. Some synthetic coumarin analogs have been engineered to display synergistic effects when combined with other natural antioxidants, suggesting potential applications in nutraceutical formulations and

functional foods[123]. Overall, the versatile antioxidant mechanisms of coumarin derivatives position them as valuable multifunctional agents in therapeutic and preventive medicine.

Anticancer potential

Coumarin derivatives have emerged as promising scaffolds in the development of anticancer agents due to their versatile chemical structures, ability to interact with diverse molecular targets, and favorable pharmacokinetic profiles[124]. Structurally, coumarins possess a benzopyrone core that can be easily modified through functional group substitutions, enabling fine-tuning of their biological activity. These modifications can significantly influence lipophilicity, target specificity, and cell permeability, thereby enhancing their cytotoxic potential against various cancer cell lines[125]. The anticancer effects of coumarin derivatives have been documented across a wide spectrum of malignancies, including breast, lung, colon, prostate, and hematological cancers, highlighting their broad therapeutic scope[126].

The molecular mechanisms underlying the anticancer activity of coumarin derivatives are multifaceted, as recorded in **Table 3**. Many of these compounds exert pro-apoptotic effects by activating intrinsic and extrinsic apoptotic pathways, often through modulation of caspases, Bcl-2 family proteins, and p53 signaling[127]. Others disrupt cancer cell proliferation by arresting the cell cycle at specific checkpoints such as G0/G1 or G2/M, interfering with cyclin-dependent kinase activity[128]. Some coumarin derivatives have demonstrated the ability to inhibit angiogenesis by downregulating vascular endothelial growth factor expression, thereby limiting tumor blood supply and metastatic potential. Additionally, certain derivatives can modulate key signaling cascades such as PI3K/Akt/mTOR, MAPK/ERK, and NF-κB, which are frequently dysregulated in cancer progression[129].

Another important feature of coumarin-based anticancer agents is their capacity to overcome multidrug resistance, a major challenge in chemotherapy. By inhibiting efflux transporters like P-glycoprotein or modulating drug-metabolizing enzymes, coumarin derivatives can restore the sensitivity of cancer cells to conventional chemotherapeutics[130]. Furthermore, their antioxidant properties help mitigate oxidative stress-induced DNA damage, indirectly supporting cancer prevention and progression control[131]. Some coumarins have also been explored as dual-function molecules—combining cytotoxic activity with photodynamic or photothermal effects—making them suitable for targeted cancer therapies with reduced systemic toxicity[132].

Given their natural abundance, synthetic accessibility, and ability to selectively target cancer-related pathways, coumarin derivatives continue to attract significant attention in drug discovery pipelines[133]. Ongoing research is focused on optimizing their potency, selectivity, and safety through rational drug design and nanotechnology-based delivery systems[134]. These advancements hold the potential to translate coumarin-derived molecules from promising preclinical candidates to clinically approved anticancer therapeutics[135].

Table 3. Representative coumarin derivatives with reported anticancer activities and their molecular mechanisms.

Coumarin derivative	Cancer type(s)	Primary mechanism(s) of action	Ref.
Umbelliferone	Breast and colon	Induces apoptosis via p53 activation and inhibits cyclin-dependent kinases	[121]
Warfarin	Breast and melanoma	Inhibits tumor cell adhesion and metastasis through suppression of AXL receptor tyrosine kinase signaling	[136,137]
8-Methoxypsoralen	Melanoma and psoriasis-related lesions	DNA intercalation and cross-linking upon UVA activation, in addition to induce apoptosis	[138]
Osthole	Lung, colorectal, and hepatocellular carcinoma	Suppresses PI3K/Akt/mTOR and MAPK pathways and inhibits angiogenesis	[139]
Esculetin	Pancreatic and colon	Induces G0/G1 cell cycle arrest and downregulates β-catenin and cyclin D1	[140]
Scopoletin	Breast and leukemia	Modulates NF-κB signaling and promotes mitochondrial-dependent apoptosis	[141]

Coumarin derivative	Cancer type(s)	Primary mechanism(s) of action	Ref.
Coumarin–chalcone hybrids	Prostate and ovarian	Dual inhibition of tubulin polymerization and topoisomerase II, in addition to cell cycle arrest at G2/M	[142]
4-Methylumbelliferone	Hepatocellular carcinoma and pancreatic	Inhibits hyaluronan synthesis and suppresses tumor invasion as well as metastasis	[143,144]
Benzocoumarins	Cervical, ovarian, and breast	ROS-mediated apoptosis and inhibition of STAT3 activation	[145–147]
Bergapten	Prostate and leukemia	Reversible β-lactamase inhibition (chemosensitization) and induction of apoptosis	[148]

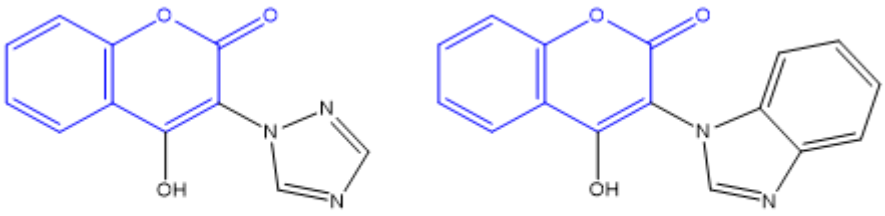
Table 3. (*Continued*)

UVA: Ultraviolet A radiation (315-400 nm); PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3.

6. Biomedical applications of coumarin derivatives

The anticancer potential of coumarin derivatives is strongly influenced by their structural features, with specific substitutions modulating their activity[149]. The broad pharmacological relevance of these molecules, combined with the relative simplicity of their synthesis, has driven increasing interest in environmentally benign preparation methods, such as green catalysis or solvent-free protocols[150]. Coumarins have also been integrated into biosensors for the detection of toxic compounds, capitalizing on their fluorescence and photostability[151].

An example of their synthetic versatility is the preparation of novel coumarin derivatives via *in situ* oxidative coupling of 4-hydroxycoumarin with azoles, using hydrogen peroxide as an oxidizing agent in an aqueous medium. The reaction efficiency is enhanced by chloroacetic acid, yielding (1*H*-1,2,4-triazole-1-yl)-4-hydroxy-4*H*-chromen-2-one and α-(benzimidazole-1-yl)-4-hydroxy-4*H*-chromen-2-one (**Figure 4**) when 1,2,4-triazole[152] or benzimidazole[153] is employed, respectively. Additionally, photosensitive unsaturated coumarin-based compounds serve as modern dual-curing agents and are widely applied as optical brighteners for fibers owing to their pronounced fluorescence[154]. Coumarin derivatives also engage in functional transformations, such as reactions between 4-hydroxycoumarin and 3-substituted acetate derivatives—like 3-mercaptoacetic acid or 3-nitroacetic acid—where the reaction pathway is dictated by the nature of the substituents[155]. These chemical and biological attributes underscore the enduring significance of coumarins in both applied and fundamental research.



(1*H*-1,2,4-triazole-1-yl)-4-hydroxy-4*H*-chromen-2-one

(Benzimidazole-1-yl)-4-hydroxy-4H-chromen-2-one

Figure 4. Chemical structures of various coumarin derivatives produced by the reaction of 4-hydroxycoumarin and azoles with chloroacetic acid as a catalyst.

Drug delivery systems

Over the years, sustained research efforts have elevated coumarin derivatives from simple organic molecules to clinically valuable therapeutics, now widely incorporated into pharmaceutical formulations. Contemporary studies increasingly focus on their broad pharmacological potential and versatility in drug

delivery systems, encompassing antimicrobial[156], antioxidant[157], antidiabetic[158], and anticancer[159] properties. The rational design of coumarin derivatives often involves strategic modification of the coumarin scaffold through the incorporation of biologically active heterocycles or functional substituents[160]. These structural innovations have given rise to coumarin-based hybrid conjugates with diverse and enhanced pharmacological profiles. Despite these advances, there remains a lack of comprehensive reviews linking the biomedical applications of coumarin derivatives to the principles and methodologies of chemical engineering[161]. Recognizing the role of chemical engineering in optimizing synthesis pathways, refining characterization techniques, and improving pharmacological performance highlights an important interdisciplinary pathway for advancing the biomedical utility of coumarins[162].

Therapeutic agents

One of the notable pharmacological features of coumarins is their capacity to protect against tumor initiation and progression, largely attributed to their potent hydroxyl radical scavenging ability. As phenolic compounds, coumarins can neutralize a wide range of free radicals and chain-propagating oxidants—capabilities that surpass some conventional antioxidants such as carotenoids and vitamin E[163]. Their diverse biological profile includes antimicrobial, anti-inflammatory, anticoagulant, antioxidant, anticancer, and anti-HIV activities[164].

Despite this wide therapeutic potential, the natural abundance of coumarins is relatively low, limiting their large-scale extraction from plant sources. This scarcity has encouraged the development of efficient synthetic routes that employ readily available starting materials under practical laboratory conditions[165]. Coumarin synthesis strategies are generally classified into conventional and green approaches. Conventional methodologies include well-established reactions such as the Knoevenagel condensation, Pechmann condensation, Perkin reaction, Reformatsky reaction, Wittig condensation, Baylis–Hillman reaction, and Suzuki–Miyaura coupling, among others. In recent years, advances in synthetic chemistry have shifted towards greener protocols aimed at minimizing the use of hazardous solvents, reagents, and catalysts, improving atom economy, and integrating sustainability principles[166].

From a microbiological standpoint, coumarins can directly disrupt microbial cell structures by inducing oxidative damage to the cell wall, inhibiting cell division, and in some cases, intercalating with DNA to interfere with replication processes[167]. Structure–activity relationship studies reveal that hydroxylated, methoxylated, and other substituted coumarins often demonstrate marked antimicrobial potency against a variety of clinically relevant human pathogens[168]. Such multifunctional bioactivities underscore the importance of coumarins as promising scaffolds for drug discovery and therapeutic innovation[169].

7. Integration of chemical engineering in drug development

Chemical engineering serves as a cornerstone in advancing biomedical applications, particularly in the synthesis of bioactive compounds. Understanding the kinetic and thermodynamic principles governing chemical reactions provides the framework for optimizing both the synthesis and structural modification of target molecules[170]. Variations in reaction pathways, operational parameters, and by-product removal strategies offer critical insights into reaction rates, equilibrium behavior, and process efficiency[171]. In industrial-scale pharmaceutical production, considerations such as safety, product quality, environmental sustainability, and cost-effectiveness are essential to ensure feasible large-scale manufacturing[172]. By integrating knowledge of reaction kinetics and thermodynamics into reaction engineering and process design, the mass production of pharmacologically significant coumarin derivatives can be achieved, thereby contributing to innovative and efficient drug development[173].

Process design

Chemical engineering principles—such as reaction kinetics, process optimization, and scale-up—play a pivotal role in advancing the development of coumarin derivatives for biomedical applications[174]. Reaction kinetics focuses on understanding the rate at which chemical transformations occur and how these rates are influenced by factors such as temperature, pressure, catalysts, and reactant concentrations. By fine-tuning these parameters, researchers can maximize conversion efficiency, paving the way for cost-effective and reliable large-scale synthesis of coumarin-based drugs[175].

Process optimization, in this context, involves applying systematic engineering strategies to design, monitor, and control chemical production in a manner that enhances yield, minimizes resource consumption, and reduces manufacturing costs[176]. In modern drug discovery, the synthesis of a diverse library of molecules is often necessary to identify candidates with promising therapeutic potential. This requires adjusting reaction conditions to enable rapid, high-throughput production while ensuring that each compound meets the desired chemical and pharmacokinetic profiles[177]. For a candidate drug to progress to clinical trials, it must be produced in sufficient quantities with consistent quality and purity. Therefore, integrating chemical engineering methodologies into the synthesis pipeline of coumarin derivatives is not only beneficial but essential[178]. Such integration bridges laboratory research and industrial manufacturing, accelerating the journey from bench-scale innovation to biomedical application.

Scale-up techniques

The scale-up process serves as a crucial bridge between laboratory research and full-scale industrial production, encompassing pilot-scale synthesis, downstream processing, toxicological evaluation, and economic feasibility studies[179]. While conventional synthetic approaches to coumarin derivatives have successfully enhanced their chemical properties and expanded reaction diversity, transitioning to industrial-scale manufacturing requires more efficient, reproducible, and economically viable production strategies[180]. Integrating chemical engineering principles into this process enables the fine-tuning of operational parameters, ultimately facilitating the sustainable and cost-effective biosynthesis of coumarin derivatives[181].

In practice, scale-up activities commence with pilot-plant synthesis and comprehensive characterization of the target compounds. Reaction conditions are systematically optimized to achieve maximum conversion rates, high yields, and improved productivity[182]. Downstream operations—such as washing, crystallization, and drying—are carefully designed and validated for industrial suitability. Safety evaluations incorporate *in vitro* cytotoxicity assays, such as the MTT cell viability test, to assess potential toxicological risks[183]. The process culminates in a detailed economic assessment, estimating production costs and market potential. Collectively, these steps streamline the development pipeline, paving the way for coumarin-based drug candidates to progress toward commercialization and biomedical application[184].

8. Case studies on coumarin derivatives

Nutraceuticals—bioactive nutrients that contribute to health promotion and disease prevention—have attracted significant scientific interest, particularly for their potential in cancer prevention. Among these, polyphenols such as flavonoids and coumarins stand out as potent plant- and fungus-derived antioxidants[185]. Their diverse biological activities encompass antiallergenic, anti-inflammatory, antibacterial, antifungal, antiviral, and anticancer effects, along with beneficial roles in inhibiting platelet aggregation, inducing vasodilation, and reducing blood pressure[186]. Structurally, coumarins are defined by a benzopyrone core and are widely distributed in plant families such as Rutaceae, Polygonaceae, and Umbelliferae[187]. Hydroxylated coumarins occur either in their free form, as glycosides, or linked to additional heterocyclic systems such as furan, pyran, or benzopyran rings[188]. They can be isolated from various plant and fungal tissues—including

roots, stems, leaves, and seeds—are naturally present in certain wines, and may also be obtained through diverse synthetic methodologies[189].

Successful applications

The development of novel therapeutics for market availability is often constrained by fundamental chemical engineering principles and practical considerations. Translating advances in chemical knowledge into viable pharmaceutical technologies can be costly, presenting significant challenges for the industry[190]. Integrating the principles of green chemistry into drug research and manufacturing offers a sustainable pathway to address these issues. This approach emphasizes environmentally responsible strategies across the entire drug lifecycle, from discovery to production, while also discouraging unsafe or unethical practices[191].

Drug discovery begins with identifying a biologically active molecule and thoroughly evaluating its pharmacokinetic properties and toxicity profile[192]. A solid understanding of the synthetic routes to lead compounds, along with potential structural modifications, can greatly reduce the time and financial investment required to bring a new therapeutic to market. Ideally, synthetic processes should employ mild reaction conditions, affordable and stable reagents, non-toxic solvents, and methods designed to minimize waste generation[193]. Moreover, rigorous screening of drug candidates enables the selection of compounds with high biological activity, optimal target selectivity, and minimal adverse effects, thereby improving both the safety and efficacy of emerging therapeutics[194].

Coumarin and its derivatives are considered an important source of bioactive compounds, and their role in medicinal chemistry plays a major role in the development of activities. A range of pharmacological and biological activities, such as antimicrobial[195], anticancer[196], antioxidant[197], anti-inflammatory[198], and anti-HIV properties[199], have been described for coumarin derivatives. Their chemical entities exhibit topical use and suitable fluorescence properties; their conjugation with fluorescent compounds enhances cell-imaging applications[200]. Recent studies on novel coumarin derivatives have been designed and synthesized, exhibiting photophysical properties and antibacterial activities toward Gram-positive and -negative bacteria[201]. These properties encourage the investigation of additional applications of coumarin derivatives, such as their role in the development of drug-delivery systems, including hydrogel, polymer-drug conjugates, micelles, liposomes, microcapsules, and others[202].

Challenges faced

The integration of chemical engineering principles can play a pivotal role in enhancing the biomedical applicability of coumarin derivatives. However, due to their varied toxicological profiles, these compounds require comprehensive preclinical toxicological assessments, followed by rigorous safety evaluations and clinical trials, before they can be adopted in medical practice[203]. Over recent decades, the growing demand for therapies that promote longevity, coupled with the increasing prevalence of chronic diseases, has placed unprecedented pressure on healthcare systems. Nature continues to serve as a rich source of bioactive agents, with coumarins representing a prime example of plant-derived phenolic compounds with potent antioxidant and antimicrobial properties[204]. While some naturally occurring coumarins may present mild or moderate toxicity, many are considered safe or exhibit negligible toxicity, making them promising candidates for pharmaceutical development. Furthermore, their suitability for drug delivery applications lies in their ability to modulate metabolic processes and control the release and bioavailability of therapeutic agents, thereby enhancing efficacy while minimizing adverse effects[205].

9. Future perspectives in coumarin research: a chemical engineering outlook

The future of coumarin research lies in deepening the integration between medicinal chemistry and chemical engineering to create scalable, efficient, and environmentally responsible production routes. As demand grows for multifunctional therapeutics that address complex diseases, chemical engineering

principles—such as reaction kinetics optimization, process intensification, and green manufacturing—could be central to transforming coumarin derivatives from promising laboratory entities into clinically approved drugs. Continuous-flow synthesis, catalytic process enhancement, and the use of renewable feedstocks offer clear pathways to more sustainable production while maintaining pharmaceutical-grade quality.

Emerging nanotechnology-based strategies, particularly in drug delivery, represent a promising frontier. Coumarin derivatives can be engineered into smart delivery systems—such as polymeric nanoparticles, dendrimers, and lipid-based carriers—that provide targeted release, improved bioavailability, and real-time fluorescence tracking of drug distribution. Chemical engineers can leverage mass transfer modeling, encapsulation kinetics, and controlled-release system design to maximize therapeutic efficiency and minimize systemic toxicity. Additionally, incorporating coumarins into meta-structured materials, such as responsive hydrogels or multi-layered nano-coatings, could expand their use in regenerative medicine, bio-sensing, and image-guided therapy.

Advancements in computational chemical engineering, including process simulation, molecular modeling, and artificial intellegence-assisted optimization, could accelerate coumarin research by predicting reaction outcomes, screening structural analogs, and minimizing trial-and-error experimentation. These tools can be combined with life-cycle assessment to ensure that coumarin manufacturing aligns with green chemistry goals, reducing waste and environmental impact. The adoption of digital twins in coumarin production facilities could further enhance process control, quality assurance, and regulatory compliance.

From a translational perspective, the next decade should focus on bridging the gap between bench-scale synthesis and industrial-scale production. This could require coordinated efforts in pilot-plant trials, techno-economic analysis, and regulatory pathway planning. Moreover, coupling pharmacokinetic modeling with process optimization can streamline the development of coumarin-based formulations tailored for specific therapeutic targets. By synergizing the creative potential of medicinal chemistry with the precision and scalability of chemical engineering, future coumarin research is poised to deliver innovative, sustainable, and patient-centered biomedical solutions.

10. Conclusion

Coumarin derivatives, as structurally versatile 1,2-benzopyrone-based compounds, continue to attract significant attention due to their diverse pharmacological properties, including antimicrobial, antioxidant, and anticancer activities. Advances in both conventional and green synthetic methodologies—such as the Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions, alongside solvent-free, biocatalytic, and microwave-assisted protocols—have enabled the preparation of structurally diverse analogues with improved bioactivity and sustainability. Comprehensive characterization using spectroscopic and chromatographic techniques ensures the structural integrity, purity, and functionality of these derivatives, laying the foundation for their biomedical applications.

The integration of chemical engineering principles into coumarin research has proven indispensable in bridging laboratory-scale innovation with industrial-scale production. Reaction kinetics, thermodynamic optimization, process intensification, and scale-up strategies not only enhance yield and reproducibility but also align with environmental and economic sustainability goals. Furthermore, chemical engineering plays a pivotal role in the design of advanced drug delivery systems, including nanoparticles, hydrogels, and polymer–drug conjugates, which improve bioavailability, target specificity, and therapeutic efficacy.

Despite these advancements, the clinical translation of coumarin derivatives requires rigorous toxicological assessment, safety profiling, and adherence to regulatory standards. Interdisciplinary collaboration between medicinal chemists, pharmacologists, and chemical engineers will be essential to overcoming these challenges. By uniting sustainable synthesis, precise characterization, and engineering-

driven process optimization, coumarin-based therapeutics hold strong promise for next-generation biomedical applications, ultimately contributing to more effective, targeted, and environmentally responsible healthcare solutions.

Conflict of interest

The authors declare no conflict of interest.

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