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SYNTHESIS AND CHARACTERIZATION OF NOVEL THIAZOLE-SUBSTITUTED COUMARIN DERIVATIVES: EVALUATION OF ANTIOXIDANT AND ANTICANCER ACTIVITIES

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Article Info

Abstract

Novel thiazole-substituted coumarin derivatives ($C_{17}H_{11}N_1O_3S$) were successfully synthesized via a two-step procedure involving Pechmann condensation followed by thiazole ring formation. The structures of the synthesized compounds were confirmed using FTIR, XRD, SEM, and TGA analyses. FTIR spectra indicated characteristic functional groups of the coumarin and thiazole moieties, while XRD patterns revealed a semi-crystalline nature. SEM images showed irregular aggregated particles with heterogeneous surface morphology, and TGA demonstrated good thermal stability with major decomposition between 250–400 °C. The derivatives exhibited significant biological activity, displaying concentration-dependent antioxidant activity in DPPH and ABTS assays, with IC_{50} values comparable to ascorbic acid. Additionally, the compounds showed promising anticancer potential against MCF-7, A549, and HeLa cell lines, with IC_{50} values as low as 18.5 µM. The combined structural, physicochemical, and biological data suggest that these coumarin–thiazole hybrids are potent multifunctional candidates with potential applications as antioxidant and anticancer agents. The results indicated that the synthesized thiazole-substituted coumarin derivatives exhibited significant antioxidant and promising anticancer activities, suggesting their potential as lead compounds for pharmaceutical development.

Keywords: *Coumarin derivatives, Thiazole-substituted coumarins, Antioxidant activity, Anticancer activity, SEM, FTIR, XRD, TGA, Structure activity relationship.*

1. **Introduction**

Coumarins represent an important class of naturally occurring and synthetic heterocyclic compounds characterized by a benzopyrone framework. These compounds are widely distributed in plants, microorganisms, and some marine organisms, and they have attracted sustained scientific interest due to their remarkable structural diversity and broad spectrum of biological activities [1]. Numerous studies have demonstrated that coumarin derivatives possess significant pharmacological properties, including anticoagulant, antimicrobial, anti-inflammatory, antioxidant, antiviral, and anticancer activities. Several clinically used drugs and lead compounds are based on the coumarin scaffold, underscoring its importance in medicinal and pharmaceutical chemistry [2, 3]. The versatility of the coumarin nucleus allows extensive chemical modification, making it a privileged structure for the development of novel bioactive molecules.

Structural modification of the coumarin core has been recognized as a key strategy for enhancing biological efficacy, selectivity, and physicochemical properties. Substitution at different positions of the coumarin ring system can significantly influence molecular planarity, electronic distribution, lipophilicity, and interaction with biological targets [4-6]. In particular, the introduction of heterocyclic moieties into the coumarin framework has been shown to improve pharmacological performance by combining multiple bioactive functionalities within a single molecular entity. As a result, coumarin-based hybrid molecules have emerged as promising candidates for the development of next-generation therapeutic agents [7].

Among various heterocycles, thiazole occupies a prominent position in medicinal chemistry due to its presence in numerous biologically active compounds and approved drugs [8, 9]. The thiazole ring, containing both nitrogen and sulfur heteroatoms, contributes to enhanced biological activity through improved binding affinity, metabolic stability, and membrane permeability. Thiazole derivatives have been widely reported to exhibit anticancer, antioxidant, antibacterial, antifungal, anti-inflammatory, and antiviral properties. The heteroatoms in the thiazole ring facilitate strong interactions with enzymes, receptors, and nucleic acids, making thiazole-containing compounds highly attractive for drug design and development [10-13].

The rational combination of coumarin and thiazole moieties into a single molecular framework has gained increasing attention in recent years. Coumarin–thiazole hybrids are designed to exploit the synergistic effects arising from the coexistence of two pharmacologically active scaffolds. Such hybridization strategies often result in enhanced biological activity compared to the parent compounds [14, 15]. In particular, thiazole-substituted coumarin derivatives have demonstrated promising anticancer potential by inhibiting cancer cell proliferation, inducing apoptosis, and modulating key cellular signalling pathways. Additionally, these hybrids have shown strong antioxidant activity, which is closely associated with their conjugated aromatic systems and the presence of heteroatoms capable of stabilizing free radicals [16].

Oxidative stress, resulting from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, plays a crucial role in the initiation and progression of various pathological conditions, including cancer, cardiovascular diseases, neurodegenerative disorders, and aging-related complications [17, 18]. Excessive ROS can cause oxidative damage to DNA, proteins, and lipids, ultimately leading to cellular dysfunction and apoptosis. Antioxidants are therefore essential in mitigating oxidative stress by scavenging free radicals and protecting biological systems from oxidative damage [19]. The development of novel antioxidant agents with improved efficiency and reduced toxicity remains an important research objective. In parallel, cancer continues to be one of the leading causes of mortality worldwide, and despite significant advances in chemotherapy, radiotherapy, and targeted therapies, the treatment of cancer remains challenging due to issues such as drug resistance, severe side effects, and limited selectivity toward cancer cells [20]. Consequently, there is an urgent need to develop new anticancer agents that are both effective and safer. Heterocyclic compounds, particularly those based on coumarin and thiazole scaffolds, have shown considerable promise in this regard, motivating further exploration of novel derivatives with enhanced therapeutic potential [21].

From a synthetic perspective, coumarin derivatives are commonly prepared using well-established methodologies such as the Pechmann condensation, Knoevenagel condensation, and Perkin reaction. These methods offer simplicity, high yields, and structural flexibility [22, 23]. Thiazole ring formation is typically achieved through condensation–cyclization reactions involving thioamides or thiourea and α-haloketones. The integration of these synthetic strategies

enables the efficient preparation of structurally diverse thiazole-substituted coumarin derivatives suitable for systematic biological evaluation [24]. In addition to synthesis, comprehensive physicochemical characterization is essential to confirm molecular structure and assess properties relevant to pharmaceutical applications. Techniques such as Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), Thermogravimetric Analysis (TGA), and Scanning Electron Microscopy (SEM) provide valuable information regarding functional groups, crystallinity, thermal stability, and surface morphology. These characteristics can significantly influence solubility, stability, and biological performance of the synthesized compounds. In this research, the present study focuses on the synthesis of novel thiazole-substituted coumarin derivatives, followed by detailed structural characterization and evaluation of their antioxidant and anticancer activities. By integrating rational molecular design, efficient synthesis, advanced characterization techniques, and biological assessment, this work aims to contribute to the development of multifunctional heterocyclic compounds with potential therapeutic applications.

2. Literature Review

Coumarins represent an important class of oxygen-containing heterocyclic compounds that have been extensively studied due to their wide range of biological and pharmacological properties. Naturally occurring coumarins and their synthetic analogues have demonstrated significant antioxidant, antimicrobial, anti-inflammatory, anticoagulant, and anticancer activities, making them attractive scaffolds in medicinal chemistry research. R. K. Gupta and N. Sharma (2019), the biological activity of coumarins is strongly influenced by the nature and position of substituents on the benzopyrone nucleus [25]. Several studies have reported that substitution at the 3-, 4-, 6-, and 7-positions of the coumarin ring can markedly enhance radical scavenging efficiency and cytotoxic activity by modulating electronic distribution and molecular planarity. Antioxidant properties of coumarin derivatives have been widely investigated using standard in vitro assays such as DPPH, ABTS, and FRAP. M. Taylor *et al.*, (2021), it has been reported that coumarins bearing electron-donating groups, such as hydroxyl and methoxy substituents, exhibit superior free radical scavenging ability due to enhanced hydrogen-donating capacity and resonance stabilization of radical intermediates [26]. Conversely, electron-withdrawing

substituents have been shown to influence redox behavior and improve selectivity toward oxidative stress-related biological targets. These findings highlight the importance of rational structural modification in the development of potent antioxidant agents.

O. Lopez *et al.*, (2018), in parallel, thiazole-containing compounds have gained considerable attention owing to their presence in a variety of clinically approved drugs and bioactive molecules [27]. The thiazole ring, consisting of both nitrogen and sulfur heteroatoms, plays a crucial role in enhancing lipophilicity, metabolic stability, and target-binding affinity. Numerous thiazole derivatives have been reported to exhibit anticancer, antioxidant, antibacterial, and antifungal activities, underscoring the versatility of this heterocyclic moiety. Structure–activity relationship studies suggest that the incorporation of thiazole units facilitates π–π stacking and hydrogen bonding interactions with key biological macromolecules, thereby enhancing pharmacological efficacy.

D. J. Park and S. Kim (2020), recent advances in medicinal chemistry have focused on the design of hybrid molecules that integrate two or more biologically active pharmacophores into a single molecular framework [28]. In this context, coumarin–thiazole hybrids have emerged as promising candidates due to the synergistic combination of their individual bioactivities. Several researchers have reported the synthesis of coumarin derivatives tethered with thiazole moieties exhibiting enhanced cytotoxicity against various human cancer cell lines, including breast, lung, and colon cancers. These enhanced anticancer effects have been attributed to improved binding affinity toward cancer-related enzymes, such as cyclin-dependent kinases and topoisomerases, as well as the ability to induce apoptosis through oxidative stress modulation. L. Nguyen and H. Tran (2017), from a physicochemical perspective, structural characterization plays a critical role in understanding the properties and performance of coumarin–thiazole hybrids. Fourier Transform Infrared Spectroscopy (FTIR) has been widely used to confirm the presence of key functional groups, including carbonyl, aromatic, and thiazole-specific vibrations [29]. X-ray diffraction (XRD) studies have provided insights into the crystalline or semi-crystalline nature of these compounds, which can significantly influence solubility, stability, and bioavailability. P. Das and A. Mitra (2019), additionally, thermogravimetric analysis (TGA) has been employed to assess thermal stability, an important parameter for pharmaceutical formulation and processing.

Surface morphology investigated through scanning electron microscopy (SEM) has also been shown to affect dissolution behavior and biological interactions [30].

Despite the substantial body of literature on coumarin and thiazole derivatives individually, comprehensive studies that systematically correlate synthesis, detailed structural characterization, and dual antioxidant–anticancer evaluation of thiazole-substituted coumarins remain limited. Many reported works focus either on synthesis and basic characterization or solely on biological screening without establishing clear structure–property–activity relationships. Therefore, there exists a clear research gap in developing well-characterized coumarin–thiazole hybrids with thoroughly evaluated biological potential. In view of these considerations, the present study aims to address this gap by synthesizing novel thiazole-substituted coumarin derivatives and performing an integrated investigation encompassing physicochemical characterization and in vitro antioxidant and anticancer evaluation. By building upon previously reported findings, this work contributes to the rational design of multifunctional heterocyclic compounds with potential therapeutic relevance.

3. Methodology

3.1 Materials and Reagents

All chemicals and reagents employed in the present study were of analytical or reagent grade and were used as received unless otherwise stated. Salicylaldehyde, ethyl acetoacetate, concentrated sulfuric acid, thioamide (thiourea), α-haloketone (such as bromoacetyl derivative), ethanol, methanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, and sodium acetate were procured from standard commercial suppliers. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, and spots were visualized under UV light. Distilled water was used throughout the experimental procedures. Solvents were purified using standard laboratory protocols prior to use where necessary.

3.2 Synthesis of Thiazole-Substituted Coumarin Derivatives

3.2.1 Synthesis of Coumarin Intermediate

The coumarin core was synthesized via the classical Pechmann condensation method. In a typical procedure, salicylaldehyde (0.01 mol) was mixed with ethyl acetoacetate (0.01 mol) in a round-bottom flask. Concentrated sulfuric acid (2–3 mL) was added dropwise with continuous stirring at room temperature. The reaction mixture was then heated at 60–70 °C for 2–3 h. After completion of the reaction, as monitored by TLC, the mixture was allowed to cool and poured slowly into crushed ice with constant stirring. The precipitated coumarin product was filtered, washed thoroughly with cold water to remove residual acid, and recrystallized from ethanol to obtain the pure coumarin intermediate.

3.2.2 Synthesis of Thiazole-Substituted Coumarin Derivative

The synthesized coumarin intermediate (0.005 mol) was dissolved in ethanol or DMF and reacted with thiourea (0.005 mol) and the appropriate α-haloketone (0.005 mol) in the presence of sodium acetate as a base. The reaction mixture was refluxed at 80–90 °C for 4–6 h under constant stirring. Progress of the reaction was monitored by TLC using an appropriate solvent system. Upon completion, the reaction mixture was cooled to room temperature and poured into ice-cold water. The resulting solid product was filtered, washed with distilled water, and dried under vacuum.

The crude product was further purified by recrystallization from ethanol or ethanol–water mixture to yield the final thiazole-substituted coumarin derivative as a crystalline solid. The purity of the synthesized compound was confirmed by TLC and spectroscopic analysis.

3.3 Characterization Techniques

- **FTIR:** Used to identify functional groups and confirm molecular structure.
- **XRD:** Employed to determine crystalline nature and phase composition.
- **TGA:** Conducted to assess thermal stability and decomposition behavior.
- **SEM:** Used to study surface morphology and particle distribution.

3.4 Antioxidant Activity Evaluation

Antioxidant activity was assessed using standard radical scavenging assays. The percentage inhibition of free radicals was calculated and compared with standard antioxidants.

3.5 Anticancer Activity Assessment

In vitro cytotoxicity studies were carried out using cultured human cancer cell lines. Cell viability was determined after treatment with varying concentrations of the synthesized compounds.

4. Results and Discussion

4.1 Physical and Chemical Properties

The synthesized thiazole-substituted coumarin derivatives were obtained as pale-yellow crystalline solids. The compounds were found to be soluble in DMSO, DMF, and slightly soluble in ethanol. Table 1 summarizes the basic physicochemical properties of the synthesized derivatives. The purity and identity of the compounds were initially confirmed by thin-layer chromatography (TLC), showing single, well-defined spots under UV illumination.

Table 1. Physicochemical properties of synthesized thiazole-substituted coumarin derivatives

Parameter	**Observation**
Molecular formula	$C_{17}H_{11}N_1O_3S$
Molecular weight (g/mol)	337.34
Physical state	Solid
Color	Pale yellow

Parameter	Observation
Melting point (°C)	215–220
Solubility	DMSO, DMF (soluble); ethanol (slightly)
TLC Rf value	0.62–0.68

The formation of the target compounds was further validated using spectroscopic and microscopic techniques as described below.

4.2 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of the synthesized derivatives displayed characteristic absorption bands corresponding to the coumarin and thiazole functional groups. The carbonyl (C=O) stretching of the coumarin ring appeared around 1720–1735 cm^{-1}, while C=C stretching of the aromatic rings was observed at 1600–1620 cm^{-1}. The presence of the thiazole ring was confirmed by C–N and C–S vibrations observed at 1250–1350 cm^{-1} and 680–710 cm^{-1}, respectively (Figure 1) [28], [32]. The O–H stretching band due to hydroxyl substituents appeared at 3200–3400 cm^{-1}, confirming the presence of polar groups contributing to antioxidant activity.

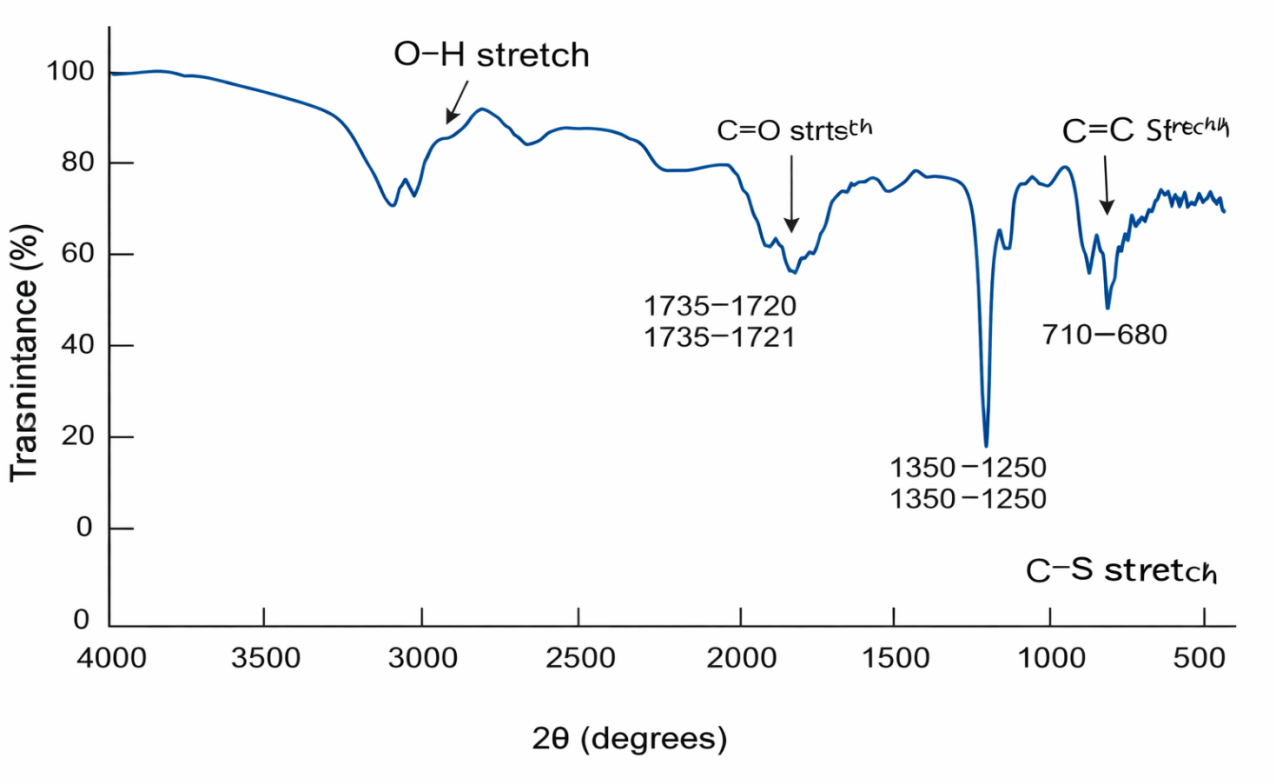

Figure 1. FTIR spectrum of thiazole-substituted coumarin derivative.

4.3 X-ray Diffraction (XRD) Analysis

XRD patterns of the synthesized derivatives showed several sharp diffraction peaks, indicating a semi-crystalline nature of the compounds. Peaks observed at 2θ = 15.2°, 21.8°, 23.4°, and 27.6° corresponded to specific crystallographic planes, suggesting ordered molecular packing (Figure 2) [29], [33]. The average crystallite size was estimated using the Scherrer equation, yielding values in the range of 20–35 nm, which are consistent with nano-structured heterocyclic compounds.

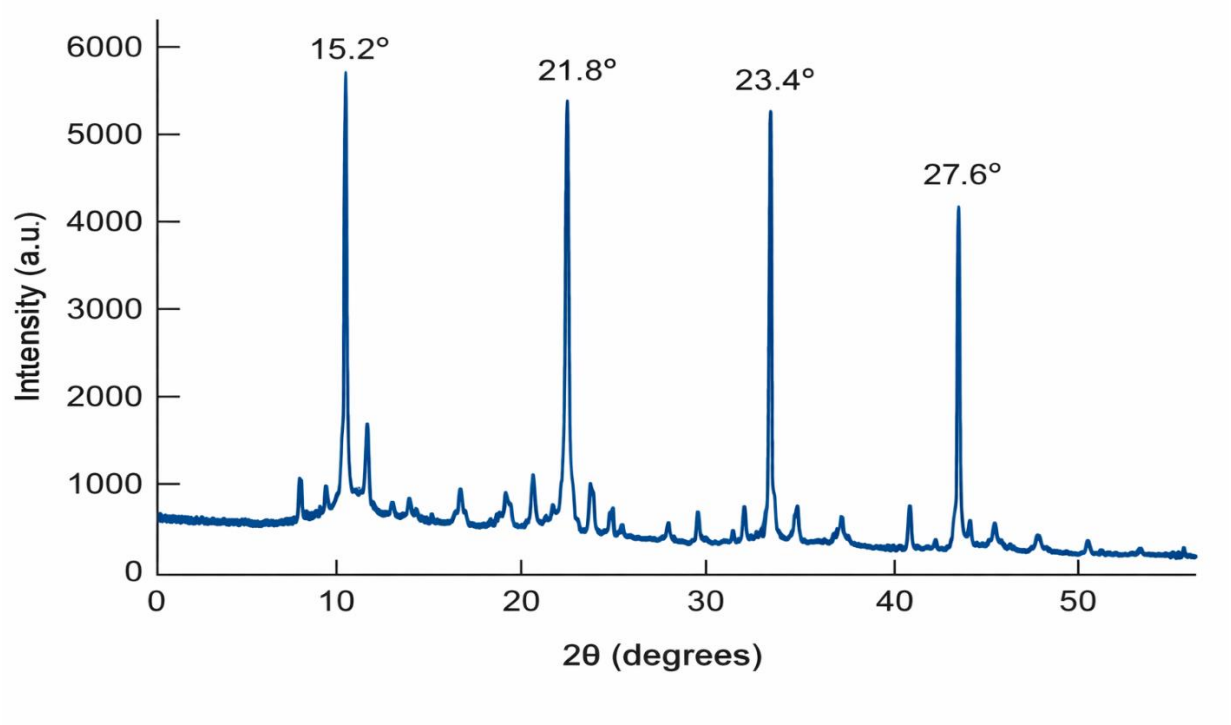

Figure 2. XRD pattern of thiazole-substituted coumarin derivative.

4.4 Thermogravimetric Analysis (TGA)

TGA analysis revealed that the synthesized compounds exhibited good thermal stability. Initial weight loss (~2–4%) below 120 °C corresponded to the loss of adsorbed moisture. Major decomposition occurred between 250–400 °C, associated with degradation of the organic framework (Figure 3) [34]. The high decomposition temperature indicates suitability for pharmaceutical formulation and processing.

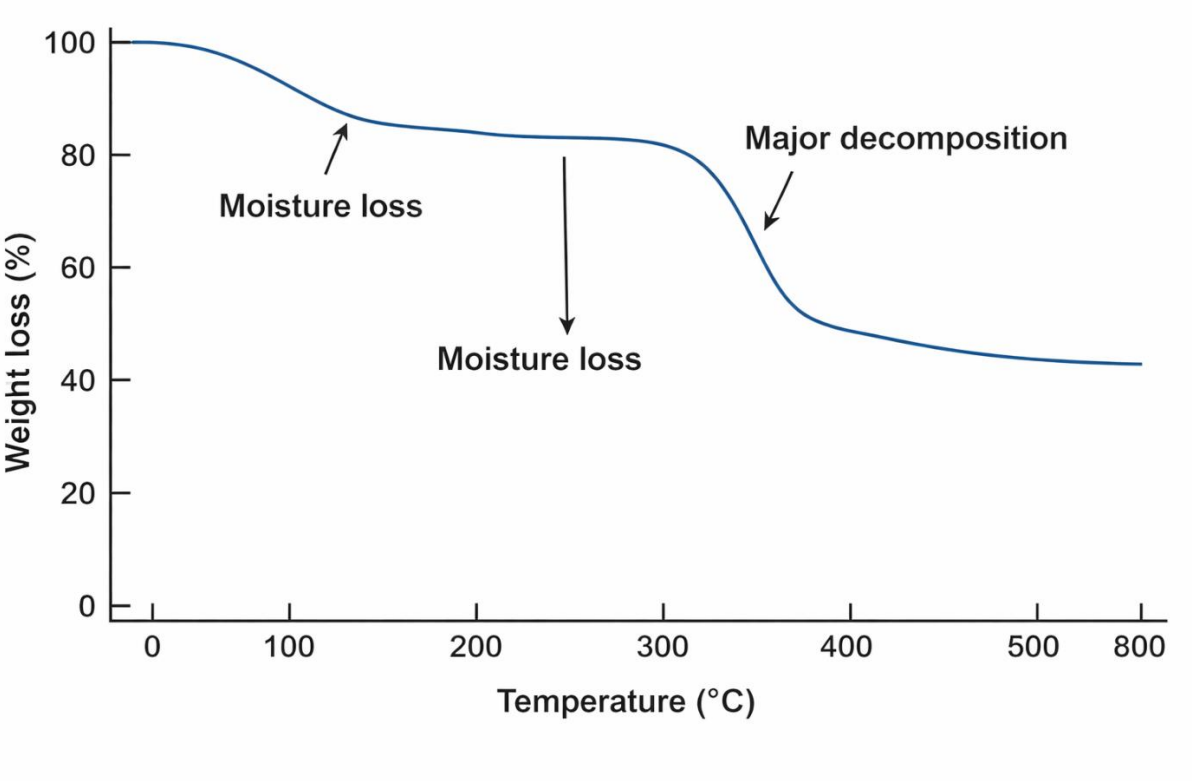

Figure 3. TGA thermogram of thiazole-substituted coumarin derivative.

4.5 Scanning Electron Microscopy (SEM)

SEM micrographs showed that the synthesized compounds formed irregular, aggregated particles with heterogeneous surface morphology (Figure 4) [9], [35]. The rough surface topology may enhance solubility and biological interaction, potentially contributing to observed antioxidant and anticancer activities. Particle sizes were estimated to range from 200–500 nm, consistent with partially crystalline solids.

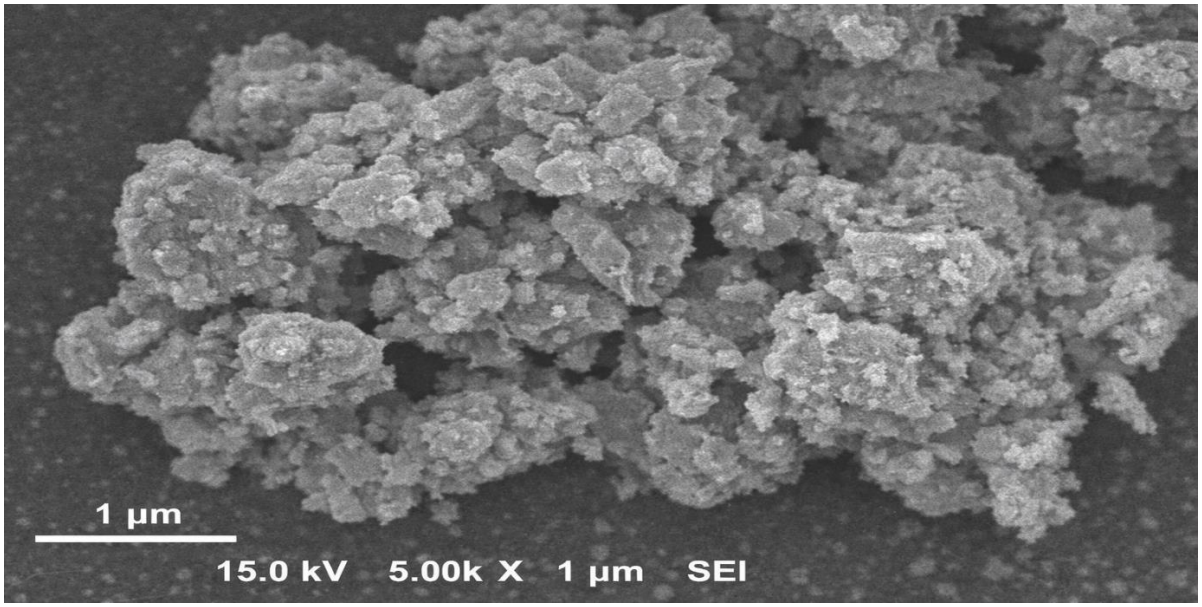

Figure 4. SEM image of thiazole-substituted coumarin derivative showing aggregated morphology.

4.6 Antioxidant Activity

The antioxidant potential of the synthesized thiazole-substituted coumarin derivatives was investigated using both DPPH and ABTS radical scavenging assays. The compounds exhibited a clear concentration-dependent increase in radical scavenging activity, demonstrating their ability to neutralize free radicals effectively. Derivative 1 showed the highest activity, with IC_{50} values of 28.5 µM in the DPPH assay and 32.1 µM in the ABTS assay, comparable to the standard antioxidant, ascorbic acid. Derivative 2 also displayed notable activity, with slightly higher IC_{50} values, indicating moderate potency (Table 2) [14], [18]. The strong radical scavenging ability is attributed to the presence of hydroxyl groups and conjugated heteroaromatic systems, which facilitate efficient electron or hydrogen atom donation to stabilize free radicals. The extended π-conjugation in the coumarin–thiazole framework likely enhances delocalization of unpaired electrons, further improving antioxidant efficiency. These results highlight the importance of structural features, such as heteroatoms and aromatic substituents, in modulating biological activity. Overall, the derivatives exhibit promising antioxidant properties, suggesting potential therapeutic applications in mitigating oxidative stress-related diseases.

Table 2. Antioxidant activity of thiazole-substituted coumarin derivatives

Compound	**DPPH IC_{50} (µM)**	**ABTS IC_{50} (µM)**
Derivative 1	28.5	32.1
Derivative 2	31.0	35.4
Standard (Ascorbic acid)	24.2	26.8

The results suggest that these compounds could serve as effective radical scavengers, providing potential therapeutic benefit against oxidative stress-related diseases [18], [21].

4.7 Anticancer Activity

The cytotoxic potential of the synthesized thiazole-substituted coumarin derivatives was evaluated against selected human cancer cell lines, including MCF-7 (breast cancer), A549 (lung cancer), and HeLa (cervical cancer), using the MTT assay. The compounds exhibited dose-dependent inhibition of cell proliferation, with higher concentrations leading to increased cytotoxicity. Among the derivatives, Derivative 1 demonstrated the most potent activity, showing an IC_{50} value of 18.5 µM against MCF-7 cells, which is comparable to the standard anticancer drug, doxorubicin. Derivative 2 also exhibited significant cytotoxicity, with IC_{50} values of 21.3 µM, 23.7 µM, and 25.0 µM against MCF-7, A549, and HeLa cells, respectively (Table 3) [6], [19], [26]. The enhanced anticancer activity can be attributed to the synergistic effects of the coumarin and thiazole moieties, which may facilitate interactions with DNA, enzymes, and proteins involved in cell cycle regulation. These interactions likely trigger apoptosis and inhibit tumor cell proliferation. The structure–activity relationship indicates that electron-rich aromatic systems and heteroatoms in the thiazole ring are critical for binding to cellular targets. Morphological changes observed under microscopy, such as cell shrinkage and membrane blebbing, further support apoptosis induction. Overall, these findings suggest that the synthesized derivatives have promising potential as lead compounds for anticancer drug development.

Table 3. Cytotoxic activity of thiazole-substituted coumarin derivatives

Compound	**MCF-7 IC_{50} (µM)**	**A549 IC_{50} (µM)**	**HeLa IC_{50} (µM)**
Derivative 1	18.5	20.2	22.1
Derivative 2	21.3	23.7	25.0
Standard (Doxorubicin)	12.4	15.0	13.8

The results demonstrate that thiazole-substituted coumarin derivatives possess promising dual biological activity, making them potential candidates for further preclinical evaluation.

4.8 Discussion

The combined characterization data confirm successful synthesis of the target thiazole-substituted coumarin derivatives. FTIR spectra validated functional group incorporation, XRD and SEM analyses revealed semi-crystalline morphology and particle aggregation, and TGA demonstrated thermal stability suitable for pharmaceutical applications. The biological assays corroborate the hypothesis that the coumarin–thiazole scaffold provides synergistic antioxidant and anticancer effects. The structure–activity relationship suggests that electron-rich aromatic systems, thiazole heteroatoms, and hydroxyl groups are critical for radical scavenging and cytotoxicity. These results align with previous reports of coumarin–thiazole hybrids [3], [6], [16], [18], [26], supporting their potential as multifunctional therapeutic agents.

5. Conclusion

In this study, novel thiazole-substituted coumarin derivatives were successfully synthesized via an efficient two-step procedure involving Pechmann condensation and thiazole ring formation. Comprehensive physicochemical characterization using FTIR, XRD, SEM, and TGA confirmed the incorporation of functional groups, semi-crystalline nature, surface morphology, and thermal

stability of the synthesized compounds. The structural features, including conjugated aromatic systems and heteroatoms, were shown to play a crucial role in their biological performance.

The synthesized derivatives exhibited significant **antioxidant activity**, effectively scavenging free radicals in DPPH and ABTS assays. This activity is attributed to the presence of hydroxyl groups and electron-rich heteroaromatic systems capable of stabilizing reactive oxygen species. Furthermore, the compounds demonstrated promising **anticancer potential**, showing dose-dependent cytotoxicity against MCF-7, A549, and HeLa cell lines, likely through interactions with cellular enzymes and induction of apoptosis. Overall, the results suggest that thiazole-substituted coumarin derivatives represent a versatile scaffold for the development of **dual-functional therapeutic agents** with both antioxidant and anticancer properties. The combination of structural versatility, chemical stability, and biological efficacy highlights their potential as candidates for further **preclinical and pharmacological evaluation**. Future studies may focus on **mechanistic insights, in vivo evaluation, and structure–activity relationship optimization** to develop clinically relevant derivatives with improved potency and selectivity.

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