Journal of Medicinal and Chemical Sciences 5 (2022) 546-560

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Synthesis and Biomedical Activities of Coumarins Derived From Natural Phenolic Acids

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ARTICLE INFO

Article history

Received: 2022-01-26
Received in revised: 2022-02-07
Accepted: 2022-02-08
Manuscript ID: JMCS-2201-1403
Checked for Plagiarism: **Yes**
Language Editor:
Ermia Aghaie
Editor who approved publication:
Dr. Behrooz Maleki

DOI:10.26655/JMCHEMSCI.2022.4.10

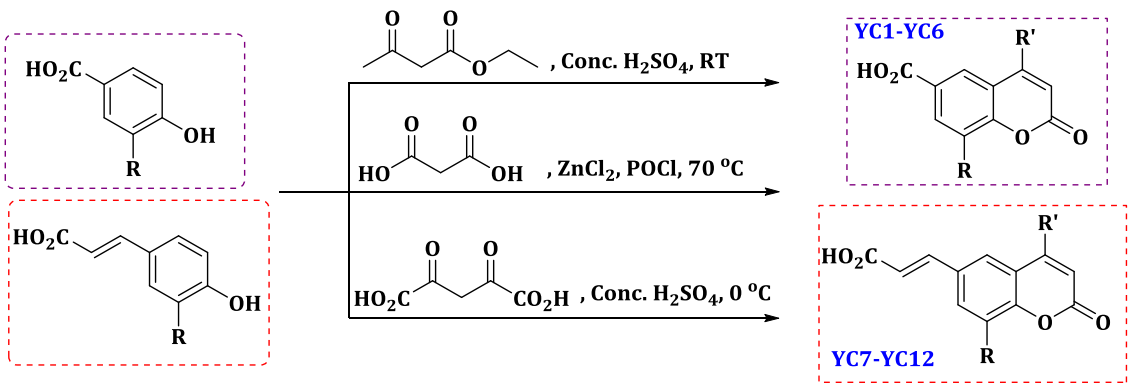
KEYWORDS

Natural phenolic acids
Semisynthetic coumarins
Antioxidant
Anti-Inflammatory
Antidiabetic
Anticancer
Cytotoxicity

ABSTRACT

The incidence of many human disorders, such as cancer, oxidative stress, diabetes mellitus, and inflammatory diseases, has been mountingly increased because of many factors, including environmental pollution, static lifestyle, and unhealthy feeding. In an attempt to explore a scaffold with multiple biomedical activities, four natural phenolic acids, namely vanillic-, protocatechuic-, ferulic-, and caffeic-acid, were selected to construct twelve derived coumarins. The skeletal formulas of the semi-synthesized coumarins were confirmed by analyzing their spectra afforded via various spectrophotometers. The biomedical characteristics of these coumarins were investigated and included their antioxidant, anti-inflammatory, antidiabetic, and anticancer activities. The antioxidant activity was quantified by monitoring the potential of these coumarins to reduce DPPH and hydroxyl oxidants and provide an electron in the redox reaction. The anti-inflammatory activity was detected by specifying the inhibitory and selectivity of these coumarins on two COX isozymes. The antidiabetic activity was determined by examining the capacity of these coumarins to suppress two enzymes involved in blood glucose regulation. The anticancer activity and cytotoxicity were examined via MTT-based methodology versus four cancer cell lines and one normal cell line. The findings revealed that the semi-synthesized coumarins exhibited potent antioxidant and anticancer activities with low-induced cytotoxicity. Also, these coumarins showed modest antidiabetic potential and inhibitory effects versus the COX isozymes, with some selectivity toward the inhibition of COX-2. The authors concluded that these coumarins, specifically **YC11**, provide a valid structural template for synthesizing multi-functional agents effective in treating health situations in which oxidative stress, inflammation, diabetes, and cancer are combined.

GRAPHICAL ABSTRACT



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Introduction

Plants and their components have been utilized as popular medicines in various parts of the world since ancient times [1]. Phenolic acids, one of the most common forms of plant phenolics, are abundant in the human diet, particularly in fruits, vegetables, and beverages. Phenolic acids have been extensively studied for their antioxidant, antibacterial, anticancer, anti-inflammatory, antidiabetic, antiviral, antifungal, and other medicinal properties [2]. The term "phenolic acid" refers to a phenol ring with one or more carboxylic acid side chains [3], and phenolic acids may be divided into two types: hydroxybenzoic acid and hydroxylcinnamic acid [4].

Vanillic acid (**VA**, 4-hydroxy-3-methoxybenzoic acid) is found in large quantities in vanilla beans and various food items, such as grapes, guava, sherry, cereal grains, green tea, and juices [5]. Many experimental studies have demonstrated this natural phenolic acid's anti-inflammatory activity by inhibiting the synthesis of numerous inflammatory mediators [6] without inducing gastric lesions or liver damage [7]. VA's antioxidant, anti-hyperglycemic, and neuroprotective properties have also been found to protect against streptozotocin-induced diabetic neuropathy [8]. Inhibiting hypoxia-inducible factor 1 in various human cancer cell lines indicated that **VA** had the anticancer potential [9].

Protocatechuic acid (**PA**, 3,4-dihydroxybenzoic acid) is widely distributed and present in bran, grain, brown rice, onions, and many fruits [10]. The antioxidant, antibacterial, anticancer, antiulcer, antidiabetic, anti-aging, antiviral, anti-inflammatory, analgesic, and nephron-protective properties are among the various pharmacological properties of this natural bioactive acid [11]. **PA**'s antioxidant properties are thought to be because it can increase the activity of numerous natural antioxidant enzymes while decreasing the activity of several endogenous oxidases [12]. **PA** also has chemo-preventive potential since it can inhibit chemical carcinogenesis and has pro-apoptotic and antiproliferative actions in the investigated cancer cell lines [13].

Citrus fruits, apples, juices, cereal grains, bran, and, most notably, coffee contain caffeic acid (**CA**, 3,4-dihydroxycinnamic acid) [14]. As a potent antioxidant, **CA** has been shown to reduce lipoperoxyl radicals (ROO•) by donating a hydrogen atom to its equivalent hydroperoxide, thus terminating the lipid peroxidation chain reaction [15]. Studies have shown **CA-rich** meals to protect against carcinogenesis by inhibiting the development of hazardous nitro-containing compounds such as nitrosamines and nitrosamides [16]. **CA** may also improve insulin sensitivity by lowering hepatic glucose production and suppressing pro-inflammatory cytokines [17]

Ferulic acid (**FA**, -hydroxy-3-methoxycinnamic acid) is a naturally occurring phenolic acid found in rice, wheat, barley, oranges, coffee, apples, and peanuts [18]. Many research findings have shown that **FA** plays an essential role as an anti-inflammatory agent, suppressing the production of pro-inflammatory cytokines, promoting the production of anti-inflammatory cytokines, and increasing the expression of stress-responsive genes and antioxidant molecules like metallothioneins [19]. Moreover, this natural acid's anticancer effect is linked to its capacity to decrease reactive oxygen species, which shields cellular components from oxidative damage [20]. Furthermore, **FA** treatment of diabetic rats was observed to restore normal blood glucose and insulin levels [19].

Coumarins are one of the most prominent families of oxygen-based heterocycles, and they have been widely used for medical and industrial applications [21]. Coumarin the class's prototype, was initially isolated from Tonka bean (*coumaru*) by Vogel in 1820, giving rise to the word “coumarin” [22]. Despite having a benzopyran-2-one nucleus, coumarins differ in the presence and placement of substituents [23–25]. Coumarins may be found in a wide range of natural sources and can also be prepared through a range of chemical interactions [26]. The majority of natural and synthetic coumarin-based compounds studied have demonstrated encouraging biomedical potential, such as antimicrobial [27], antiparasitic [28], anti-inflammatory [29], antioxidant [30], antithrombotic [31], anti-Alzheimer [32],

antitumor [33], anticonvulsant , antipsychotic, analgesic, and antiviral activities [34].

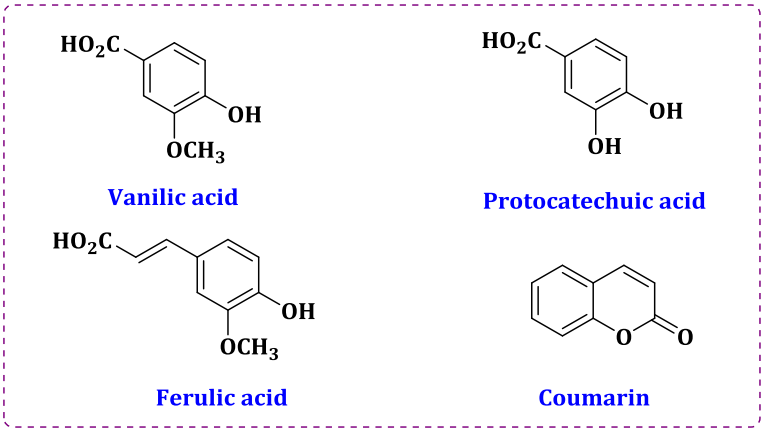


Figure 1: The chemical structures of the natural phenolic acids used in this work and the coumarin nucleus

This work aimed to explore a coumarin-based scaffold with multi-biomedical activities. To fulfill this target, four natural phenolic acids, specifically vanillic, protocatechuic, ferulic, and caffeic acids, were adopted as precursors for the synthesis of twelve derived coumarins, denoted by the letters **YC1**-**YC12**. Their biomedical properties were also studied, including antioxidant, anti-inflammatory, antidiabetic, anticancer, and cytotoxicity.

Materials and Methods

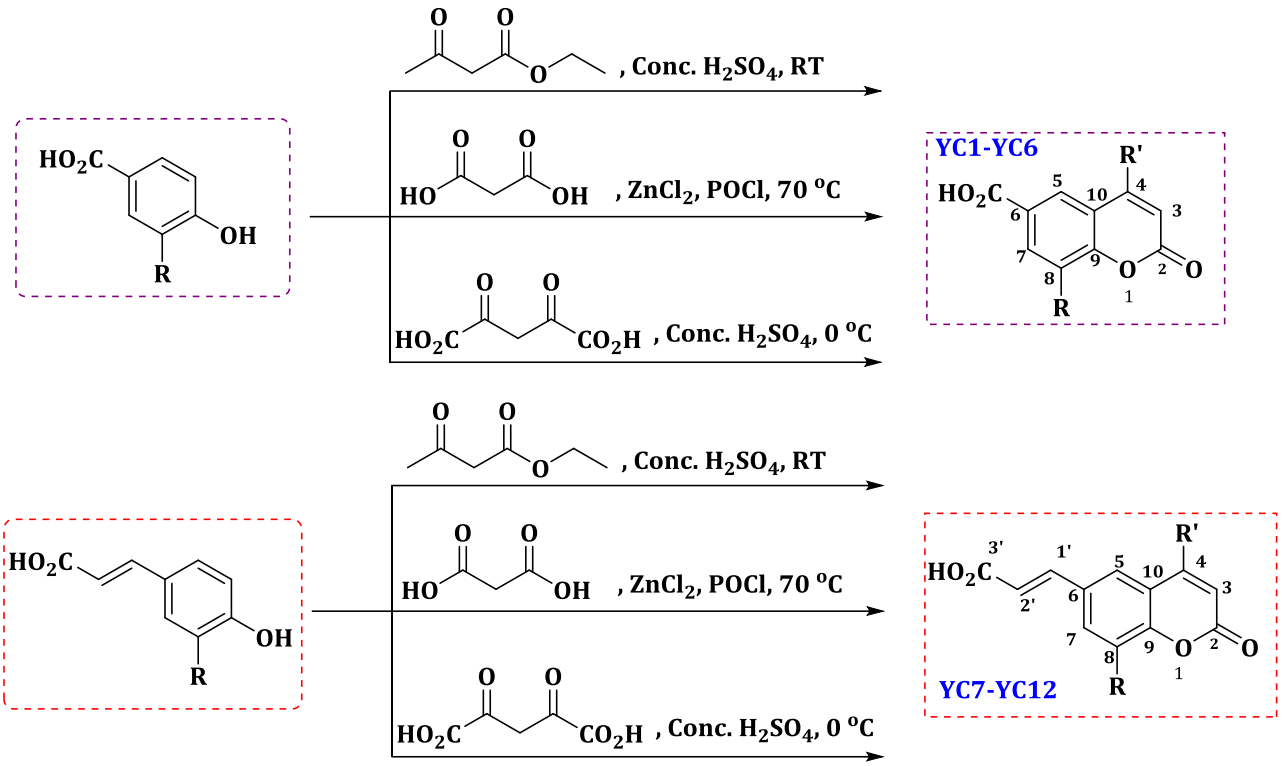
Chemicals and Instruments

The biological evaluating systems with their supplementary reagents and chemicals employed to synthesize the phenolic acid-derived coumarins were purchased from several international suppliers. These sources were Scharlau, Cayman Chemical, Sigma-Aldrich, Labcorp, Chem-Lab, Bioworld, Haihang, and others. The synthesized compounds' melting temperatures (mp) were reported utilizing the electrothermal's IA9300 digital melting temperature equipment and open-capillary methodology. Thin-layer chromatography (TLC) was utilized to check the complete synthesis status and determine the integrity of the generated coumarins. This procedure's moveable and fixed phases were a membrane filter Sigma TM TLC-Silica Gel 60 (F254) and a diethyl ether: MeOH (4:1) mixture. The Bruker Avance 3 HD 600 and 150 MHz (DMSO-d6), Bruker FTIR-alpha-ATR, and Cary 300 UV-Vis Bioanalytical grade spectrophotometers were used to establish the ^{1}HNMR, ^{13}CNMR, IR, and λ_{max} electromagnetic ranges of the synthesized phenolic acid-derived coumarins.

Synthetic Skeletal Pathway

The steps constructing the skeletal pathway for synthesizing the natural phenolic acid-derived coumarins (**YC1**-**YC12**) are illustrated in Scheme 1. The substituents of the parent natural phenolic acids, their corresponding synthesized coumarins, and the time required to complete the synthesis are recorded in
Table **1**.

Under the action of thermal, phenolic acid (25 mmol) was solubilized in ethyl acetoacetate (3.44 mL, 27 mmol). The resulting solution was dropped to a pre-chilled concentrated H_2SO_4 (25 mL) in an ice bath for 30 min. By regulating the addition rate, the reaction temperature was kept below 10 °C. The reaction mixture was repeatedly agitated for a particular time, as recorded in Table 1, at room temperature (RT), then poured over a smashed ice-H_2O combination, forcefully agitated, and filtered. The raw was collected through filtration, rinsed with cold H_2O, and recrystallized using 70% EtOH [35].



Scheme 1: Synthetic pathway for constructing the phenolic acid-derived coumarins (YC1-YC12)

Table 1: The substituents of the parent and synthesized compounds and the time needed to complete the synthesis

Natural phenolic acid	R	Reaction time (hr)	Coumarin symbol	R	R'
VA	OCH_3	16.5	**YC1**	OCH_3	CH_3
		9.4	**YC2**		OH
		13.7	**YC3**		CH_2COOH
PA	OH	16.0	**YC4**	OH	CH_3
		10.2	**YC5**		OH
		13.9	**YC6**		CH_2COOH
FA	OCH_3	17.8	**YC7**	OCH_3	CH_3
		10.6	**YC8**		OH
		14.5	**YC9**		CH_2COOH
CA	OH	17.1	**YC10**	OH	CH_3
		11.5	**YC11**		OH
		15.2	**YC12**		CH_2COOH

General method for synthesizing natural phenolic acid-derived 4-methlcoumarins (**YC1**, **YC4**, **YC7**, and **YC10**)

*8-Methoxy-4-methyl-2-oxo-2H-chromene-6-carboxylic acid (**YC1**):* mp= 205-208°C; λ_{max} (EtOH)= 421 nm; R_f= 0.43; %yield= 67; FTIR (ν, stretching, cm^{-1}): 3075 (C-H, alkene, lactone), 3002 (O-H, COOH), 2927 (C-H, OCH_3), 2882 (C-H, CH_3), 1737 (C=O, ester, lactone), 1702 (C=O, COOH), 1672 (C=C, alkene, lactone), 1558 (C=C, aromatic ring), and 1270, 1067 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 11.12 (s, 1H, 6-COOH), 8.26 (s, 1H, H-5), 7.60 (s, 1H, H-7), 6.44 (s, 1H, H-3), 3.94 (s, 3H, 8-OCH_3), and 2.63 (s, 3H, 4-CH_3) ppm; ^{13}C-NMR: δ= 170.8 (C, 6-COOH), 161.4 (C, C-2), 158.2 (C, C-8), 154.3 (C, C-4), 148.9 (C, C-9), 130.0 (C, C-6), 123.1 (C, C-10), 121.6 (CH, C-5), 114.3 (CH, C-7), 112.9 (CH, C-3), 50.4 (CH_3, 8-OCH_3), and 21.6 (CH_3, 4-CH_3) ppm.

*8-Hydroxy-4-methyl-2-oxo-2H-chromene-6-carboxylic acid (**YC4**):* mp= 220-222°C; λ_{max} (EtOH)= 429 nm; R_f= 0.36; %yield= 69; FTIR (ν, stretching, cm^{-1}): 3287 (O-H, phenolic), 3074 (C-H, alkene, lactone), 3004 (O-H, COOH), 2887 (C-H, CH_3), 1735 (C=O, ester, lactone), 1704 (C=O, COOH), 1670 (C=C, alkene, lactone), and 1556 (C=C, aromatic ring); ^{1}H-NMR: δ= 11.10 (s, 1H, 6-

COOH), 8.24 (s, 1H, H-5), 7.68 (s, 1H, H-7), 6.42 (s, 1H, H-3), 5.12 (s, 1H, 8-OH), and 2.61 (s, 3H, 4-CH_3) ppm; ^{13}C-NMR: δ= 170.3 (C, 6-COOH), 161.2 (C, C-2), 153.9 (C, C-8), 153.0 (C, C-4), 149.2 (C, C-9), 128.9 (C, C-6), 124.3 (C, C-10), 121.2 (CH, C-5), 117.4 (CH, C-7), 114.1 (CH, C-3), and 21.8 (CH_3, 4-CH_3) ppm.

*(E)-3-(8-Methoxy-4-methyl-2-oxo-2H-chromen-6-yl)acrylic acid (**YC7**):* mp= 266-269°C; λ_{max} (EtOH)= 465 nm; R_f= 0.49; %yield= 48; FTIR (ν, stretching, cm^{-1}): 3054 (C-H, alkene, lactone), 3000 (O-H, COOH), 2920 (C-H, OCH_3), 2877 (C-H, CH_3), 1735 (C=O, ester, lactone), 1701 (C=O, COOH), 1664 (C=C, alkene, lactone), 1543 (C=C, aromatic ring), and 1243, 1051 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 11.32 (s, 1H, H-3'), 7.57 (d, 1H, H-1', *J*= 18 Hz), 7.42 (s, 1H, H-5), 6.84 (s, 1H, H-7), 6.51 (d, 1H, H-2', *J*= 18 Hz), 6.32 (s, 1H, H-3), 3.90 (s, 3H, 8-OCH_3), and 2.62 (s, 3H, 4-CH_3) ppm; ^{13}C-NMR: δ= 173.1 (C, C-3'), 161.3 (C, C-2), 158.4 (C, C-8), 152.6 (C, C-4), 149.1 (C, C-1'), 142.2 (C, C-9), 133.9 (C, C-6), 124.1 (C, C-10), 118.7 (CH, C-2'), 116.8 (CH, C-5), 114.3 (CH, C-3), 111.9 (CH, C-7), 56.5 (CH_3, 8-OCH_3), and 21.5 (CH_3, 4-CH_3) ppm.

*(E)-3-(8-Hydroxy-4-methyl-2-oxo-2H-chromen-6-yl)acrylic acid (**YC10**):* mp= 272-275°C; λ_{max} (EtOH)= 473 nm; R_f= 0.40; %yield= 52; FTIR (ν, stretching, cm^{-1}): 3284 (O-H, phenolic), 3055 (C-H, alkene, lactone), 2998 (O-H, COOH), 2868 (C-H, CH_3), 1734 (C=O, ester, lactone), 1700 (C=O, COOH), 1667 (C=C, alkene, lactone), and 1540 (C=C, aromatic ring); ^{1}H-NMR: δ= 11.35 (s, 1H, H-3'), 7.59 (d, 1H, H-1', *J*= 18 Hz), 7.40 (s, 1H, H-5), 6.83 (s, 1H, H-7), 6.47 (d, 1H, H-2', *J*= 18 Hz), 6.34 (s, 1H, H-3), 5.15 (s, 1H, 8-OH), and 2.65 (s, 3H, 4-CH_3) ppm; ^{13}C-NMR: δ= 173.4 (C, C-3'), 161.6 (C, C-2), 154.2 (C, C-8), 153.7 (C, C-4), 149.2 (C, C-1'), 144.3 (C, C-9), 135.4 (C, C-6), 124.9 (C, C-10), 118.7 (CH, C-2'), 116.8 (CH, C-5), 114.9 (CH, C-7), 112.4 (CH, C-3), and 21.8 (CH_3, 4-CH_3) ppm.

General method for synthesizing natural phenolic acid-derived 4-hydroxycoumarins (**YC2**, **YC5**, **YC8**, and **YC11**)

A mixture of phenolic acid (0.01 mol), anhydrous zinc chloride (30 g, 0.22 mol), phosphoryl chloride (40 mL, 0.43 mol), and malonic acid (1.04 g, 0.01 mol) was heated in a thermostatic water bath maintained at 70 °C for a particular time, as recorded in Table 1. The mixture flowed to a smashed ice-H_2O combination, and the solidified material was hydrolyzed with a 10% aqueous Na_2CO_3 solution (30 mL). The filtrate was treated with an HCl, and the raw was purified by recrystallizing from EtOH [36].

*4-Hydroxy-8-methoxy-2-oxo-2H-chromene-6-carboxylic acid **(YC2)**:* mp= 212-215°C; λ_{max} (EtOH)= 428 nm; R_f= 0.38; %yield= 63; FTIR (ν, stretching, cm^{-1}): 3312 (O-H, benzylic), 3062 (C-H, alkene, lactone), 2993 (O-H, COOH), 2924 (C-H, OCH_3), 1728 (C=O, ester, lactone), 1698 (C=O, COOH), 1669 (C=C, alkene, lactone), 1567 (C=C, aromatic ring), and 1254, 1070 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 12.47 (s, 1H, 4-OH), 11.23 (s, 1H, 6-COOH), 8.45 (s, 1H, H-5), 7.76 (s, 1H, H-7), 6.34 (s, 1H, H-3), and 3.90 (s, 3H, 8-OCH_3) ppm; ^{13}C-NMR: δ= 170.7 (C, 6-COOH), 168.0 (C, C-4), 163.1 (C, C-2), 157.4 (C, C-8), 150.2 (C, C-9), 129.1 (C, C-6), 121.6 (CH, C-5), 120.1 (C, C-10), 113.9 (CH, C-7), 93.8 (CH, C-3), and 52.5 (CH_3, 8-OCH_3) ppm.

*4,8-Dihydroxy-2-oxo-2H-chromene-6-carboxylic acid **(YC5)**:* mp= 225-227°C; λ_{max} (EtOH)= 438 nm; R_f= 0.31; %yield= 68; FTIR (ν, stretching, cm^{-1}): 3287 (O-H, phenolic), 3201 (O-H, benzylic), 3060 (C-H, alkene, lactone), 2988 (O-H, COOH), 1729 (C=O, ester, lactone), 1694 (C=O, COOH), 1671 (C=C, alkene, lactone), and 1566 (C=C, aromatic ring); ^{1}H-NMR: δ= 12.44 (s, 1H, 4-OH), 11.20 (s, 1H, 6-COOH), 8.36 (s, 1H, H-5), 7.66 (s, 1H, H-7), 6.33 (s, 1H, H-3), and 5.12 (s, 1H, 8-OH) ppm; ^{13}C-NMR: δ= 170.8 (C, 6-COOH), 168.2 (C, C-4), 162.7 (C, C-2), 154.2 (C, C-8), 150.1 (C, C-9), 129.4 (C, C-6), 121.8 (CH, C-5), 119.3 (C, C-10), 117.0 (CH, C-7), and 93.7 (CH, C-3) ppm.

*(E)-3-(4-Hydroxy-8-methoxy-2-oxo-2H-chromen-6-yl)acrylic acid **(YC8)**:* mp= 274-277°C; λ_{max} (EtOH)= 475 nm; R_f= 0.41; %yield= 46; FTIR (ν, stretching, cm^{-1}): 3201 (O-H, benzylic), 3055 (C-H, alkene, lactone), 3002 (O-H, COOH), 2932 (C-H, OCH_3), 1733 (C=O, ester, lactone), 1700 (C=O, COOH), 1666 (C=C, alkene, lactone), 1549 (C=C, aromatic ring), and 1244, 1048 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 12.42 (s, 1H, 4-OH), 11.27 (s, 1H, H-3'), 7.58 (d, 1H, H-1', *J*= 18 Hz), 7.44 (s, 1H, H-5), 6.82 (s, 1H, H-7), 6.45 (d, 1H, H-

2', *J*= 18 Hz), 6.30 (s, 1H, H-3), and 3.83 (s, 3H, 8-OCH_3) ppm; ^{13}C-NMR: δ= 173.3 (C, C-3'), 168.4 (C, C-4), 163.6 (C, C-2), 158.4 (C, C-8), 149.8 (C, C-1'), 145.6 (C, C-9), 134.2 (C, C-6), 120.0 (C, C-10), 118.4 (CH, C-2'), 116.5 (CH, C-5), 112.3 (CH, C-7), 93.4 (CH, C-3), and 58.1 (CH_3, 8-OCH_3) ppm.

(E)-3-(4,8-Dihydroxy-2-oxo-2H-chromen-6-yl)acrylic acid ***(YC11)****:* mp= 280-283°C; λ_{max} (EtOH)= 484 nm; R_f= 0.37; %yield= 48; FTIR (ν, stretching, cm^{-1}): 3289 (O-H, phenolic), 3207 (O-H, benzylic), 3053 (C-H, alkene, lactone), 3001 (O-H, COOH), 1736 (C=O, ester, lactone), 1704 (C=O, COOH), 1672 (C=C, alkene, lactone), and 1542 (C=C, aromatic ring); ^{1}H-NMR: δ= 12.40 (s, 1H, 4-OH), 11.22 (s, 1H, H-3'), 7.54 (d, 1H, H-1', *J*= 18 Hz), 7.58 (s, 1H, H-5), 6.84 (s, 1H, H-7), 6.40 (d, 1H, H-2', *J*= 18 Hz), 6.32 (s, 1H, H-3), and 5.14 (s, 1H, 8-OH) ppm; ^{13}C-NMR: δ= 173.2 (C, C-3'), 168.8 (C, C-4), 163.6 (C, C-2), 154.5 (C, C-8), 150.1 (C, C-1'), 146.3 (C, C-9), 135.5 (C, C-6), 120.6 (C, C-10), 118.4 (CH, C-2'), 116.9 (CH, C-5), 114.2 (CH, C-7), and 94.2 (CH, C-3) ppm.

General method for synthesizing natural phenolic acid-derived coumarin-4-acetic acids (**YC3**, **YC6**, **YC9**, and **YC12**)

A salt-ice bath was used to chill 10 ml H_2SO_4 in a bottom flask to 0 °C. The frequency of adding citric acid powder (0.96 g, 5 mmol) to this chilly acid was decided by the reaction temperature, which should be kept under 5 °C. The reaction mixture was agitated for 30 min at 25 °C before being gradually raised to 70 °C. The formation of froth and bubbling controlled the rate of heating. The reaction mixture was placed in a salt-ice bath as a clear solution developed. The solution of phenolic acid (5 mmol) and concentrated H_2SO_4 (5 ml) was added to the agitated mixture on the condition that the reaction temperature remained below 10 °C. The reaction mass was chilled for 36 h before being filtered through an ice-water mixture. The raw was purified from impurities by recrystallizing ethyl acetate [37].

4-(Carboxymethyl)-8-methoxy-2-oxo-2H-chromene-6-carboxylic acid ***(YC3)****:* mp= 226-229°C; λ_{max} (EtOH)= 424 nm; R_f= 0.33; %yield= 71; FTIR (ν, stretching, cm^{-1}): 3043 (C-H, alkene, lactone), 2996 (O-H, COOH), 2938 (C-H, OCH_3), 2852 (C-H, alkyl), 1733 (C=O, ester, lactone), 1700 (C=O, COOH), 1674 (C=C, alkene, lactone), 1588 (C=C, aromatic ring), and 1225, 1014 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 11.20 (s, 1H, 6-COOH), 11.01 (s, 1H, 4-CH_2COOH), 8.18 (s, 1H, H-5), 7.82 (s, 1H, H-7), 6.40 (s, 1H, H-3), 3.94 (s, 3H, 8-OCH_3), and 3.12 (s, 2H, 4-CH_2) ppm; ^{13}C-NMR: δ= 173.7 (C, 4-CH_2COOH), 170.4 (C, 6-COOH), 161.3 (C, C-2), 158.5 (C, C-8), 156.1 (C, C-4), 149.3 (C, C-9), 129.4 (C, C-6), 122.8 (C, C-10), 120.2 (CH, C-5), 114.0 (CH, C-7), 112.6 (CH, C-3), 51.3 (CH_3, 8-OCH_3), and 38.4 (CH_2, 4-CH_2COOH) ppm.

4-(Carboxymethyl)-8-hydroxy-2-oxo-2H-chromene-6-carboxylic acid ***(YC6)****:* mp= 240-243°C; λ_{max} (EtOH)= 438 nm; R_f= 0.26; %yield= 74; FTIR (ν, stretching, cm^{-1}): 3274 (O-H, phenolic), 3045 (C-H, alkene, lactone), 2998 (O-H, COOH), 2859 (C-H, alkyl), 1732 (C=O, ester, lactone), 1702 (C=O, COOH), 1676 (C=C, alkene, lactone), and 1590 (C=C, aromatic ring); ^{1}H-NMR: δ= 11.21 (s, 1H, 6-COOH), 11.06 (s, 1H, 4-CH_2COOH), 8.15 (s, 1H, H-5), 7.71 (s, 1H, H-7), 6.49 (s, 1H, H-3), 5.14 (s, 1H, 8-OH), and 3.12 (s, 2H, 4-CH_2) ppm; ^{13}C-NMR: δ= 173.2 (C, 4-CH_2COOH), 170.6 (C, 6-COOH), 161.5 (C, C-2), 157.4 (C, C-4), 154.6 (C, C-8), 149.4 (C, C-9), 129.3 (C, C-6), 124.1 (C, C-10), 121.3 (CH, C-5), 117.2 (CH, C-7), 112.9 (CH, C-3), and 38.3 (CH_2, 4-CH_2COOH) ppm.

(E)-3-(4-(Carboxymethyl)-8-methoxy-2-oxo-2H-chromen-6-yl)acrylic acid ***(YC9)****:* mp= 287-290°C; λ_{max} (EtOH)= 468 nm; R_f= 0.38; %yield= 42; FTIR (ν, stretching, cm^{-1}): 3059 (C-H, alkene, lactone), 3001 (O-H, COOH), 2937 (C-H, OCH_3), 2851 (C-H, alkane), 1732 (C=O, ester, lactone), 1705 (C=O, COOH), 1668 (C=C, alkene, lactone), 1541 (C=C, aromatic ring), and 1246, 1040 (C-O-C, asymmetrical ether); ^{1}H-NMR: δ= 11.25 (s, 1H, H-3'), 11.03 (s, 1H, 4-CH_2COOH), 7.52 (d, 1H, H-1', *J*= 18 Hz), 7.32 (s, 1H, H-5), 6.84 (s, 1H, H-7), 6.42 (s, 1H, H-3), 6.30 (d, 1H, H-2', *J*= 18 Hz), 3.82 (s, 3H, 8-OCH_3), and 3.11 (s, 2H, 4-CH_2) ppm; ^{13}C-NMR: δ= 173.3 (C, C-3'), 172.1 (C, 4-CH_2COOH), 161.4 (C, C-2), 158.6 (C, C-8), 156.3 (C, C-4), 149.4 (C, C-1'), 142.7 (C, C-9), 134.6 (C, C-6), 123.7 (C, C-10), 118.4 (CH, C-2'), 117.0 (CH, C-5), 114.2 (CH, C-3), 112.1 (CH, C-7), 53.6 (CH_3, 8-OCH_3), and 38.8 (CH_2, 4-CH_2COOH) ppm.

*(E)-3-(4-(Carboxymethyl)-8-hydroxy-2-oxo-2H-chromen-6-yl)acrylic acid (****YC12****):* mp= 294-297°C;

λ_{max} (EtOH)= 452 nm; R_f= 0.32; %yield= 43; FTIR (ν, stretching, cm^{-1}): 3294 (O-H, phenolic), 3062 (C-H, alkene, lactone), 3004 (O-H, COOH), 2859 (C-H, alkane), 1735 (C=O, ester, lactone), 1708 (C=O, COOH), 1666 (C=C, alkene, lactone), and 1540 (C=C, aromatic ring); ^{1}H-NMR: δ= 11.28 (s, 1H, H-3'), 11.05 (s, 1H, 4-CH_2COOH), 7.59 (d, 1H, H-1', *J*= 18 Hz), 7.34 (s, 1H, H-5), 6.80 (s, 1H, H-7), 6.42 (s, 1H, H-3), 6.31 (d, 1H, H-2', *J*= 18 Hz), 5.14 (s, 1H, 8-OH), and 3.14 (s, 2H, 4-CH_2) ppm; ^{13}C-NMR: δ= 173.5 (C, C-3'), 172.3 (C, 4-CH_2COOH), 162.2 (C, C-2), 158.4 (C, C-4), 154.3 (C, C-4), 150.1 (C, C-1'), 144.5 (C, C-9), 135.6 (C, C-6), 124.4 (C, C-10), 118.9 (CH, C-2'), 116.4 (CH, C-5), 114.9 (CH, C-7), 113.2 (CH, C-3), and 38.4 (CH_2, 4-CH_2COOH) ppm.

The Antioxidant Activity Evaluation

Using Vitamin C (**Vit. C**) as a reference, the magnitudes of the synthesized natural phenolic acid-derived coumarins for dissipating the reactive species of DPPH (1,1-diphenyl-2-picryl-hydrazyl) and hydroxide moieties and transferring an electron in the electrochemical reaction were measured. By DMSO as thinner, secondary solutions of the following eight concentrations were generated from a primary one (1 mg/mL): 500, 250, 125, 100, 50, 25, 12.5, and 6.25 µg/mL. The dissipating percent (D%) values of the supplied concentrations were determined for each investigated coumarin using the incoming mathematical law [38]:

$$\boldsymbol{D}(\%) = \boldsymbol{Abs}_{\mathbf{con}} - \boldsymbol{Abs}_{\mathbf{sam}} \div \boldsymbol{Abs}_{\mathbf{con}} \times \mathbf{100}$$

The absorptions of the control and tested sample at a specific colored wavelength were denoted by the abbreviations $\boldsymbol{Abs}_{\mathbf{con}}$ and $\boldsymbol{Abs}_{\mathbf{sam}}$, respectively.

The dissipating activity was defined as the concentration of a reference or synthesized phenolic acid-derived coumarin, at which 50% of the free radicals were dissipated, or half of the oxidized iron particles were reduced. The notation DC_{50} denoted it. This metric was created using a non-linear analysis to depict the relationship between D% values and their associated logarithmic concentrations [38].

DPPH-free Radical Dissipating Activity Assay

The investigated solution (1.5 mL) at a particular concentration was mixed with an ethanolic DPPH solution (0.5 mL, 0.1 mM). The mixed solution was overlaid with aluminum platelets to hide it from sunlight, and the covered system was kept at 25 °C for 30 min. At 517 nm, the ability of the investigated solution to erase the DPPH violet color was measured colorimetrically. Ethanolic DPPH solution (1.5 mL) plus diluting solvent, EtOH, (1.5 mL) made up the control solution [39].

Hydroxide-free Radical Dissipating Activity Assay

A predetermined concentration of the investigated solution (1.5 ml) was mixed with 2.4 ml of potassium phosphate buffer (0.2 M, pH 7.8). 60 µL of 0.001 M $FeCl_3$, 90 µL of 0.001 M pyridine [3,2-*h*] quinoline, and 150 µl of 0.16 M H_2O_2 were added to this mixture in that order. The resulting mixture was kept at 25 °C for 5 min before being colorimetrically tested at 560 nm. All of the components mentioned above were present in the control solution. However, the studied solution was replaced with the utilized buffer solution [40].

Total Reducing Capacity Assay

The investigated solution (1 mL) at a predetermined concentration was mixed with 2 ml potassium phosphate buffer (0.2 M, pH 6.6) and 2 mL aqueous $K_3[Fe(CN)_6]$ solution (1%). The mixture was held in a thermo-digital water bath at 50 °C for 20 min. After some consideration, the interaction was slowed down by adding 2 mL of aqueous CCl_3COOH solution (10%). The resulting mixture was centrifuged for 10 min at 2000 rpm. 2 mL effluent was added to a mixture of 2 mL H_2O and 0.4 mL aqueous $FeCl_3$ solution (0.01 %). The resulting mixture was maintained at 25 °C for 10 min before being colorimetrically measured at 700 nm. The reference solution was made the same way as the tested combination, while the investigated solution was replaced with the utilized buffer solution [41].

The Anti-Inflammatory Activity Evaluation

A spectrophotometric COX (ovine) inhibition monitoring evaluation system was used to test the COX1/COX2 inhibitory activity of the synthesized natural phenolic acid-derived coumarins (Kit product code 705010, Cayman Chemical, USA). Serial dilutions of the investigated compounds and controls (celecoxib, **Coxib**, and aspirin, **Asp**) were cultivated with the enzyme-phenotype at 25 °C for

5 min, starting at 0.25 µg/mL and ending at 32 µg/mL. After the gestation time and the addition of chromogenic reagent and arachidonic acid as a substrate, absorbance was measured at 590 nm using a plate reader (Victor Nivo multi-mode computer-aided microplate-scanner, PerkinElmer, USA) [42].

Antidiabetic Activity Evaluation

The *in vitro* inhibitory properties of the synthesized natural phenolic acid-derived coumarins were evaluated versus two enzyme phenotypes. Those are important in blood glucose management and include yeast α-glucosidase and porcine α-amylase. The IC_{50} value, defined as the concentration of the biochemical entity necessary to suppress the enzymatic activity by 50% at test circumstances, is used to specify this activity. Before undertaking these two experiments, different secondary concentrations of a primary solution (2 mg/mL) were produced. These concentrations were produced using a DMSO as thinner to prepare concentrations of 1000, 500, 250, 125, 100, 50, 25, 12.5, and 6.25 µg/mL [43].

Yeast α-Glucosidase Blocking Assay

In this blocking assay, two mixtures are prepared, namely the enzyme- and substrate-mixture. The first was composed of 20 µL α-glucosidase enzyme (0.1 unit/mL) in phosphate buffer solution and 20 µL specific concentration of the examined solution. The second was prepared by dissolving the test substrate, 4-nitrophenyl-α-D-glucopyranoside, in a phosphate buffer (pH 6.8) solution to achieve the concentration of 375 µg/mL. Subsequently, an equivalent volume (40 µL) of the first and second mixtures was mixed and incubated at 37 °C for 30 min. The interaction was stopped by adding an 80 µL phosphate buffer solution containing Na_2CO_3 (0.2 M) to the incubated combination. As a reference α-glucosidase inhibitor, precose was used, and the control solution was made the same way as the incubated combination. However, the examined solution was substituted with DMSO. The ability of the synthesized natural phenolic acid-derived coumarins to block the enzyme activity was measured spectrophotometrically at 405 nm, and the percentage of inhibition was estimated using the following law [43]:

$$\boldsymbol{\alpha - Glucosidase\ inhibitory}\ \% = \boldsymbol{Abs_{con} - Abs_{sam} \div Abs_{con} \times 100}$$

Porcine α-Amylase Blocking Assay

Two mixtures were prepared in this enzymatic assay, which are the enzyme- and substrate-mixture. The first was composed of 20 µL α-amylase enzyme (2 unit/mL) in phosphate buffer solution and 20 µL predetermined concentration of the examined solution. The second was prepared by dissolving the test substrate, starch, in a phosphate buffer (pH 6.8) solution to achieve 2 mL of 500 µg/mL. Subsequently, an equivalent volume (40 µL) of the first and second mixtures was mixed and incubated at 25 °C for 10 min. The interaction was stopped by adding a 2 mL of 0.4 N aqueous sodium hydroxide solution containing 3,5-dinitrosalicylic acid (1%) and anhydrous sodium potassium tartrate (12%) to the incubated combination. The resulting mixture was heated for 15 minutes in a digital boiling water bath, adjusted H_2O to 10 ml, and chilled to 25°C in an aqueous ice bucket. As a standard, precose was utilized, and the control solution was made the same way as the incubated combination, but the examined solution was substituted with DMSO. The tested solution's ability to block enzyme activity was assessed spectrophotometrically at 540 nm, and the percentage of inhibition was determined using the following law [44]:

$$\boldsymbol{\alpha - Amylase\ inhibitory}\ \% = \boldsymbol{Abs_{con} - Abs_{sam} \div Abs_{con} \times 100}$$

Anticancer Activity Evaluation

A malignant line with 1×10^4 cells was transplanted within every barrel of a microplate for 24 hrs over a growth-promoted culture. Each barrel was given independently one of the double-reduced ratios of the examined compound. The secondary concentrations of each compound varied from 200 µg/mL to 6.25 µg/mL and were generated from a primary solution (1 mg/mL) using DMSO as a diluent. A baseline cytotoxicity assay was achieved 72 h after the intervention using MTT (28 µL, 3.27×10^3 µM) as a visual marker for viable cells as the growing media was withdrawn. A microplate scanner set to 492 nm was used to determine the absorbance of each barrel after 90 min of incubation at 37 °C. Each compound's cytotoxic effect was measured as a

percentage of proliferation-retardation (PR%) equals (**Abs** $_{untreated}$ - **Abs** $_{treated}$)/**Abs** $_{untreated}$ ×100. The absorbance readings of the untreated and treated barrels were represented by the symbols **Abs** $_{untreated,}$ and **Abs** $_{treated}$, respectively. The proliferation-retardation (PR_{50}) activity was defined as the concentration of a reference or synthesized phenolic acid-derived coumarin, at which 50% of the viable cells were proliferating retarded. This variable was calculated using non-linear statistics from the graphical relationship between the values of PR% and their corresponding logarithmic concentrations [45].

Results and Discussion

Chemical Synthetic Pathway

Pechmann condensation reaction was used as a template for condensing natural phenolic acids with three different electrophile-containing chemical moieties. That included ethyl acetoacetate, malonic acid, and acetone dicarboxylic acid. Among the benzoic acid-based natural phenolic acids, **PA** afforded a higher %yield than **VA**. The authors contributed this characteristic to the presence of hydroxyl group in the ortho position to the nucleophilic moiety, phenolic hydroxyl group, which is a more potent electron-donating group than methoxy group. The same characteristic was observed when comparing the %yield of **FA** and **CA** [46]. On the other side, the acetone dicarboxylic acid was the best electrophile-containing compound and afforded the highest %yield. Ethyl acetoacetate was the second better electrophile-containing compound, followed by malonic acid [47].

Assessment of Antioxidant Activity

The research area focused on trapping the harmful free radicals has received much attention in recent medical records [48–50]. This is owing to the robust relationship between oxidative stress and various tenacious diseases, such as cancer, diabetes, and inflammatory disorders. Accordingly, the development of semisynthetic compounds from well-known natural antioxidants has piqued the attendance of the medical profession [51–53].

The characteristic of the semi-synthesized coumarins to act as antioxidant applicants was detected by monitoring their capacity to reduce DPPH and hydroxyl oxidants and provide an electron in the electron-transport redox reaction. The authors could detect various conclusions from the results summarized in

Table **2**. The first is the semi-synthesized coumarins showed a promising and potent antioxidant activity under the conditions of the used experiments. The coumarins derived from FA and CA exhibited potent activity compared with those derived from VA and PA in this field. The authors related this property to the presence of a high conjugated system in the earlier two coumarins compared with that found in the latter two compounds [54]. Secondly, the semi-synthesized coumarins (**YC10**-**YC12**) derived from **CA** had a more powerful activity than the other coumarins. The authors contributed this issue to the role of the phenolic hydroxyl group at position 8 in enhancing the conjugated capacity of the system [55]. Thirdly, the semi-synthesized coumarin symbolized **YC11** revealed the highest antioxidant activity among the other coumarin and control. Accordingly, these semisynthetic coumarins may consider as a potent antioxidant with a promising role in therapeutics. The authors connected this valuable finding to the presence of a high conjugation supported by the presence of phenolic and benzylic hydroxyl groups [56]. The fourth is the antioxidant activity of the semi-synthesized coumarins based on their electrophilic precursor has the following order: malonic acid, ethyl acetoacetate, and acetone dicarboxylic acid. The authors may attribute the limited activity of the coumarins derived from the latter compound to the presence of the acetic acid moiety at position 4. It is believed that this moiety can be considered as a poorer positive contributor in the conjugation compared with the other moieties found at the same position involving the hydroxyl and methyl functional groups [57]. Finally, the semi-synthesized coumarins and the control showed the same activity order through the three assayed methods.

Table 2: The results of three separate investigations explored the antioxidant capacity of the semi-synthesized coumarins and control

Symbol	DC_{50}±SD		
	DPPH-radical dissipating impact	Hydroxyl-radical dissipating impact	Total reducing impact
Vit. C	48.67 ± 0.69	50.31 ± 0.84	48.22 ± 0.90
YC1	73.87 ± 0.81	70.01 ± 0.88	71.12 ± 1.04
YC2	70.28 ± 0.82	67.65 ± 0.93	65.41 ± 1.02
YC3	73.67 ± 0.94	74.81 ± 0.91	73.90 ± 1.07
YC4	67.26 ± 0.96	65.07 ± 0.89	65.98 ± 0.86
YC5	65.57 ± 0.79	62.57 ± 0.91	60.42 ± 0.94
YC6	68.05 ± 0.85	69.36 ± 0.84	68.65 ± 1.02
YC7	58.12 ± 1.02	55.97 ± 0.92	56.35 ± 1.08
YC8	56.36 ± 1.05	53.38 ± 0.98	51.49 ± 0.89
YC9	59.34 ± 0.81	60.21 ± 0.98	59.22 ± 0.90
YC10	52.76 ± 0.92	51.45 ± 0.87	52.11 ± 1.00
YC11	48.12 ± 0.88	49.82 ± 0.84	47.08 ± 0.89
YC12	55.23 ± 0.76	56.27 ± 0.90	55.87 ± 0.91

DC50 was measured in µg/ml, and each investigation was performed in three independent experimental trials (n=3)

Assessment of Anti-Inflammatory Activity

The activity of the semi-synthesized coumarins as anti-inflammatory candidates was investigated versus COX-1 and COX-2 utilizing **Asp** and **Coxib** as controls. Although the activity and selectivity of the controls have been adequately reported, they were included in the current study to provide more obvious comparisons. The values that represented the activities of the semi-synthesized coumarins and controls versus COX-1 and COX-2 are listed in Table 3. Also, the values of selectivity index (**SI**), computed by dividing the scored activity versus COX-1 by the scored activity versus COX-2 are presented in this table to simplify the prediction of COX-2 selectivity (the compound with a greater **SI** value reveals the better COX-2 selectivity).

Two distinctive findings are emerged from analyzing the results are represented in Table 3. The first is the semi-synthesized coumarins, in terms of activity and selectivity, may occupy the midway between the utilized controls. The second finding is that the inhibitory effect of the applied coumarins versus COX-1 is inversely related to their antioxidant capacity, whereas the COX-2 inhibitory effect is directly connected. So, the authors related the relative inhibitory effect versus COX-2 and the selectivity of the semi-synthesized coumarins to their antioxidant potential [58].

Table 3: The estimated SI values and the scored activities of semi-synthesized coumarins and controls versus COX-1 and COX-2

Symbol	IC_{50}±SD		SI (COX-1/COX-2)
	COX-1	COX-2	
Asp	3.58 ± 0.66	29.82 ± 0.54	0.12
Coxib	7.35 ± 0.68	1.24 ± 0.47	5.93
YC1	6.12 ± 0.71	6.09 ± 0.62	1.00
YC2	6.11 ± 0.63	5.77 ± 0.56	1.06
YC3	6.31 ± 0.62	6.43 ± 0.59	0.98
YC4	6.23 ± 0.56	6.01 ± 0.67	1.04
YC5	6.19 ± 0.72	5.56 ± 0.59	1.11
YC6	6.38 ± 0.69	6.27 ± 0.66	1.02
YC7	6.33 ± 0.64	5.89 ± 0.71	1.07
YC8	6.30 ± 0.61	5.34 ± 0.73	1.18
YC9	6.44 ± 0.72	5.96 ± 0.70	1.08
YC10	6.43 ± 0.69	5.76 ± 0.47	1.12
YC11	6.45 ± 0.73	5.25 ± 0.54	1.23
YC12	6.52 ± 0.71	5.89 ± 0.47	1.11

IC50 was measured in µg/ml, and each investigation was performed in three independent experimental trials (n=3)

Assessment of Antidiabetic Activity

With significant growth in aging, poor lifestyles, and obesity, diabetes mellitus is emerging globally as one of the most dangerous, exhausting, and chronic illnesses [59]. Interfering with its pathophysiology, which involves the abnormal release of harmful free radicals, is one way to treat this abnormal metabolic condition [60]. Accordingly, the property of the semi-synthesized coumarins to act as antidiabetic applicants was investigated after measuring their antioxidant activity. This property has investigated the capacity of these semi-synthetic compounds to suppress two enzymes included in the blood-glucose regulation, specifically porcine α-amylase and yeast α-glucosidase.

Regarding the employed assays' conditions and matching to acarbose as a prototype referenced inhibitor, the authors concluded three remarkable points upon analyzing the outcome recorded in Table 4. First, the order of antidiabetic activity, regarding the semi-synthesized coumarins, was followed a matching fashion in their capacity for inhibiting the two involved enzymes [61]. Second, the semi-synthesized coumarins showed modest antidiabetic efficacy, providing a promising structural template for developing potent antidiabetic medicines. The last point is the inhibitory effect of the semi-synthesized coumarins versus the investigated enzymes is in the same direction with their antioxidant activity. Consequently, the authors could infer that the antidiabetic efficacy of these coumarins is due to their ability to act as antioxidants [62].

Table 4: The outcomes of three different runs used to investigate the antidiabetic activity of the referenced control and semi-synthesized coumarins

Symbol	IC_{50}±SD	
	α-Glucosidase inhibiting effect	α-Amylase inhibiting effect
Acarbose	281.22 ± 0.97	262.46 ± 0.94
YC1	466.17 ± 1.03	453.52 ± 0.98
YC2	463.34 ± 1.06	446.74 ± 1.01
YC3	474.05 ± 0.92	462.28 ± 1.06
YC4	455.32 ± 0.97	440.12 ± 1.04
YC5	447.51 ± 0.91	434.83 ± 0.88
YC6	459.69 ± 0.90	446.46 ± 0.89
YC7	434.54 ± 1.02	421.02 ± 1.05
YC8	428.95 ± 1.01	413.42 ± 0.97
YC9	441.03 ± 1.00	427.65 ± 0.92
YC10	422.37 ± 1.07	409.78 ± 1.04
YC11	416.08 ± 1.01	401.16 ± 0.94
YC12	429.89 ± 1.06	417.65 ± 0.92

IC_{50} was detected in µg/ml, and each study was conducted in three separated experimental trials (n=3)

Assessment of Anticancer Activity And Cytotoxicity

Using 5-fluorouracil as a standard cytotoxic drug and MTT dye as a color change marker, the preliminary property of the semi-synthesized coumarins to serve as anticancer applicants was investigated via a well-documented cell-viability methodology. Furthermore, the cytotoxicity of these coumarins on normal cells was studied using the same assayed method. Four cancer cell lines and one normal cell line were employed in this investigation. The first cell lines phenotype included AB12 (mouse malignant mesothelioma, **10092306**), MCF-7 (Caucasian breast adenocarcinoma, **86012803**), SK-OV-3 (Caucasian ovary adenocarcinoma, **91091004**), and LC540 (rat fischer leydig cell testicular tumor, **89031604**). While the second cell line phenotype is RWPE-1 (Epithelial cells from the marginal area of a histologically normal adult human prostate, **CRL-11609**).

Several deductive markers could be detected by inspecting the findings reported in Table 5. First, the semi-synthesized coumarins showed a potent anticancer activity versus the test cancer lines approximating 5-fluorouracil. Second, the rank of the anticancer activity concerning the semi-synthesized coumarins against the tested cancer cell lines was roughly similar. Third, the pattern of

this activity is approximately similar to those of the antioxidant and anti-inflammatory effects. Consequently, the authors might infer the anticancer activity of the semi-synthesized coumarins to their ability to quench harmful free radicals and suppress the inflammatory process [45,63]. Finally, the cytotoxicity of the semi-synthesized coumarins on the utilized normal cell line is inversely related to their anticancer, antioxidant, and anti-inflammatory activities and significantly lower than that of 5-fluorouracil. Based on that, the authors could conclude that these coumarins may provide a scaffold with potent anticancer activity and minimal cytotoxicity.

Table 5: The outcomes of three different runs were used to investigate the anticancer and cytotoxicity of the standard cytotoxic drug and semi-synthesized coumarins

Symbol	PR_{50}±SD				
	AB12	MCF-7	SK-OV-3	LC540	RWPE-1
5-Fluorouracil	19.34 ± 0.93	12.29 ± 0.91	22.48 ± 1.00	21.89 ± 0.89	34.87 ± 0.95
YC1	24.74 ± 0.87	14.96 ± 0.83	25.62 ± 1.09	26.03 ± 1.01	55.12 ± 0.98
YC2	24.51 ± 1.03	14.63 ± 1.02	25.17 ± 1.04	25.75 ± 1.08	56.39 ± 0.97
YC3	24.95 ± 1.06	15.09 ± 0.98	25.99 ± 0.96	26.32 ± 1.04	54.11 ± 0.97
YC4	23.80 ± 0.92	14.33 ± 0.94	25.07 ± 1.07	25.70 ± 0.93	61.58 ± 0.92
YC5	23.62 ± 0.98	14.06 ± 0.94	24.69 ± 1.02	25.44 ± 0.83	61.12 ± 0.88
YC6	24.01 ± 1.02	14.51 ± 0.96	25.42 ± 0.92	25.98 ± 0.86	59.03 ± 1.03
YC7	23.08 ± 0.98	13.86 ± 1.03	24.73 ± 0.89	25.21 ± 0.92	65.46 ± 0.94
YC8	22.89 ± 1.01	13.74 ± 1.08	24.40 ± 0.94	24.95 ± 0.94	66.12 ± 1.06
YC9	23.28 ± 1.09	14.02 ± 0.92	24.96 ± 1.06	25.46 ± 1.06	64.55 ± 0.90
YC10	22.57 ± 0.94	13.36 ± 0.99	24.41 ± 1.02	24.69 ± 1.05	67.89 ± 0.96
YC11	22.29 ± 0.91	13.35 ± 0.90	24.09 ± 1.03	24.37 ± 0.98	68.65 ± 0.92
YC12	22.76 ± 1.03	13.63 ± 0.97	24.66 ± 1.05	24.92 ± 0.95	67.57 ± 1.04

For triple-separated trials, the PR50 scores were given in µg/ml, while the SD (standard deviation) numbers were factored

Conclusions

This study successfully documented the synthesis and characterization of twelve natural phenolic acid-derived coumarins. Their biological actions were also thoroughly examined, including antioxidant, anti-inflammatory, antidiabetic, anticancer, and cytotoxicity. The impact of many structural variables on the evaluated biological activities was determined based on the findings. To start, swapping allylic carboxylic acid for position 6 in the backbones of these coumarins may improve their activity. Second, the direct link between this location and the carboxylic acid moiety may have a deleterious impact on bioactivities. Third, the presence of a benzylic hydroxyl group in the backbone of these compounds may increase their activity; however, the impact of a methyl group may be less. Fourth, the activity of these semisynthetic coumarins may be limited by the presence of an acetic acid moiety at the benzylic position. Finally, when compared to the methoxy functional group, the inclusion of the phenolic hydroxyl group at position 8 resulted in improved bioactivities. The authors stated that taking these structural aspects into account might allow the development of powerful multi-functional biological medicines. Cancer, diabetes, inflammation, and oxidative stress are among the leading health concerns that such agents can address with low cytotoxicity.

Acknowledgments

The authors are very grateful to the University of Mosul/College of Pharmacy for their provided facilities, which helped improve this work's quality. Also, the authors are grateful to Dr. Sara Firas Jasim for her attempt to improve the quality of this study.

Financial Support

The work is self-funded.

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Conflict of Interest
We have no conflicts of interest to disclose

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HOW TO CITE THIS ARTICLE
Seema Mahmood Kasim, Noora Thamer Abdulaziz, Yasser Fakri Mustafa. Synthesis and Biomedical Activities of Coumarins Derived From Natural Phenolic Acids*, J. Med. Chem. Sci.*, 2022, 5(4) 546-560
DOI: 10.26655/JMCHEMSCI.2022.4.10
URL: http://www.jmchemsci.com/article_144548.html