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Boosting 3*H*-Benzo[*f*]chromen-3-one Chalcone with Anti-inflammatory Drugs: Synthesis, Characterization, and Evaluation of Cytotoxicity and Antimicrobial Activity

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Abstract—A series of novel 3*H*-benzo[*f*]chromen-3-one derivatives bearing non-steroidal anti-inflammatory drug moieties were synthesized with good yields. Benzo[*f*]coumarin chalcone was prepared via Claisen–Schmidt condensation between 2-acetyl-3*H*-benzo[*f*]chromen-3-one and 4-hydroxybenzaldehyde in basic medium and was then esterified with carboxylic acids (drugs) in the presence of phosphoryl chloride and anhydrous zinc(II) chloride. The newly synthesized compounds were characterized by FT-IR and ^{1}H and ^{13}C NMR spectra and elemental analyses and were screened in vitro for their anticancer and antimicrobial activity. Some of the tested compounds showed a good activity in comparison to standard drugs.

Keywords: benzo[*f*]chromen-3-one, chalcone, anti-inflammatory drugs, esterification

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INTRODUCTION

Fused chromenes play a very significant role in medicinal chemistry and are used as valuable basic core for the design and synthesis of pharmacologically active compounds [1, 2]. Coumarin and its derivatives possess a wide range of biological activities such as antimicrobial [3], anticancer [4–7], anticoagulant [8], analgesic [9], ulcerogenic [10], antiviral [11], antimalarial [12], anti-inflammatory [13, 14], antidepressant [15], and antioxidant [16, 17] and inhibit HIV protease [18], acetylcholinesterase [19], monoamine oxidase B (MAO-B) [20], and steroid 5α-reductase [21]. In addition, compounds with a chalcone backbone are known to possess a wide range of biological activities [22, 23]. Many coumarin derivatives were designed and found to be promising as organic fluorescent materials for potential applications in biochemical and biological imaging due to their light emission properties [24]. In this work, we report the synthesis of a new series of benzocoumarin derivatives conjugated with anti-inflammatory drugs and their biological evaluation.

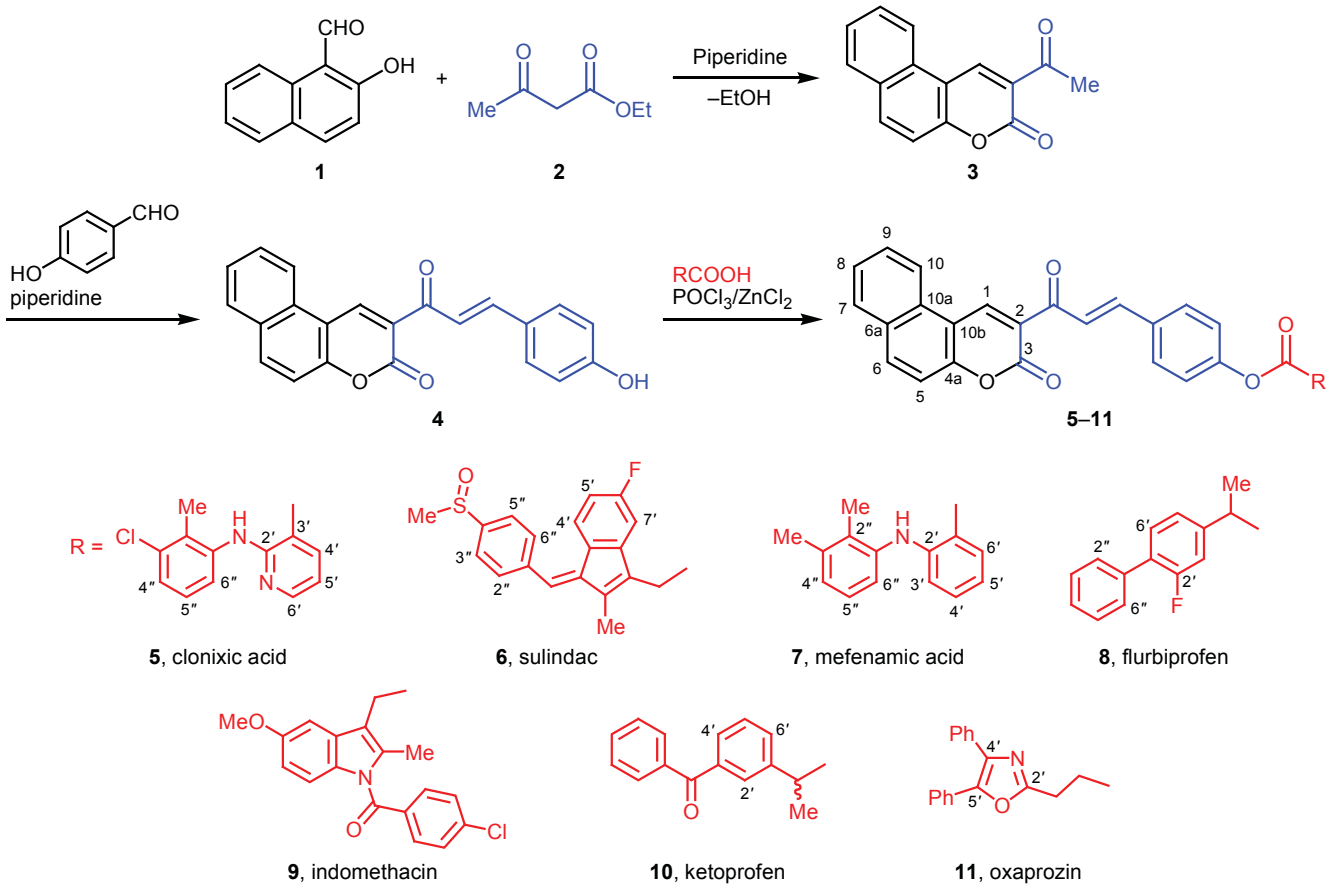
RESULTS AND DISCUSSION

Initially, we prepared 3-acetyl-5,6-benzocoumarin **3** by treatment of 2-hydroxynaphthaldehyde **1** with ethyl acetoacetate **2** in the presence of piperidine. The condensation of **3** with 4-hyroxybenzaldehyde gave benzocoumarin chalcone **4**, and the latter was coupled with anti-inflammatory drugs, namely clonixin, sulindac, mefenamic acid, flurbiprofen, indomethacin, ketoprofen, and oxaprozin) via esterification in the presence of phosphoryl chloride and anhydrous zinc chloride (Scheme 1).

The structures of **5**–**11** were determined by spectroscopic methods (FT-IR, ^{1}H and ^{13}C NMR) and elemental analyses. The FT-IR spectra of **5**–**11** showed characteristic absorption bands at 1756–1730 cm^{-1} attributed to lactone carbonyl stretching and at 1730–1715 cm^{-1} due to ester carbonyl stretching, whereas the band at 1690–1650 cm^{-1} was assigned to chalcone carbonyl stretching. Other absorption bands due to substituents present in their molecules were also observed (see Experimental).

In the ^{1}H NMR spectra of **5**–**11**, protons of the benzocoumarin moiety gave almost similar patterns.

Scheme 1.



The 1-H proton resonated as a singlet at δ 8.60–8.20 ppm, and signals in the region δ 8.24–7.84 ppm were assigned to protons of the benzene ring fused to the coumarin fragment. The enone fragment of **5**–**11** gave two doublets at δ 7.20 and 8.04 ppm, indicating *trans* configuration of the chalcone C=C double bond.

In the ^{13}C NMR spectra of **5**–**11**, the chalcone carbonyl carbon atom resonated at δ_C 175.0–168.0 ppm, and the ester and lactone carbonyl carbon signals were located at δ_C 168.0–161.0 and 162.0–159.0 ppm, respectively. The signals at δ_C 155.0–150.0 and 152.0–146.0 ppm were assigned to C^{10a} and C^1 of the benzocoumarin fragment, respectively. The double-bonded carbon atoms of the enone linkage resonated in the regions δ_C 128.0–124.5 and 145.0–138.0 ppm. The other signals were also consistent with the proposed structures (see Experimental).

Compounds **5**–**11** were screened in vitro for their antitumor activities against SK-LU-1 and MCF-7 cancer cell lines by the standard MTT assay using docetaxel as a positive control. The cell viability tests were carried out at different concentrations. Compounds **5**, **6**, **9**, and **10** at a concentration of 80 μM showed the most potent inhibition of cancer cell proliferation (Fig. 1), whereas the other compounds displayed very weak or no activity in comparison with docetaxel. The calculated IC_{50} values are presented in Table 1.

Some of the synthesized compounds displayed promising activity against both bacterial and fungal strains (Table 2). Compounds **5**, **8**, **9**, and **11** showed

Table 1. Cytotoxicity of compounds **5**–**11**

Compound no.	IC_{50}, μM	
	SK-LU-1	MCF-7
5	21.6±0.72	24.7±0.88
6	30.2±2.42	41.5±2.05
7	>100	>100
8	>100	>100
9	25.3±0.85	36.9±1.07
10	21.5±1.69	39.2±1.83
11	>100	>100
Docetaxel	25±1.35	30±1.42

Table 2. Antimicrobial activity of compounds **5-11**

Compound no.	Inhibition zone diameter, mm							
	E. coli		*S. aureus*		*C. albicans*		*A. niger*	
	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL
5	11	18	9	16	8	15	2	4
6	3	5	8	17	9	12	4	8
7	2	4	4	8	10	13	3	5
8	11	20	3	7	2	4	5	10
9	12	18	5	11	9	12	4	12
10	2	5	11	20	6	10	6	8
11	8	19	6	13	2	11	5	7
Cephalexin	12	20	14	23	11	20	13	21
Fluconazole	8	15	9	16	13	22	15	25
DMSO	0		0		0		0	

a good activity against *E. coli* at a concentration of 100 μg/mL. Compounds **5**, **6**, and **10** were also active against *S. aureus* at the same concentration. Furthermore, compounds **5**, **6**, **7**, and **9** exhibited a good inhibitory activity against *C. albicans*. However, none of the compounds tested (except for **7**) were active against *A. niger* (Table 2).

In conclusion, a series of new 5,6-benzocoumarin chalcone derivatives conjugated with anti-inflammatory drugs through an ester linkage were successfully synthesized and were screened for cytotoxicity and antimicrobial activity. The compounds containing OMe, Cl, F, and NH substituents showed good anticancer, antibacterial, and antifungal activities, and they can be regarded as potential anticancer and antimicrobial agents. Further tests are required to prove their in vivo activity.

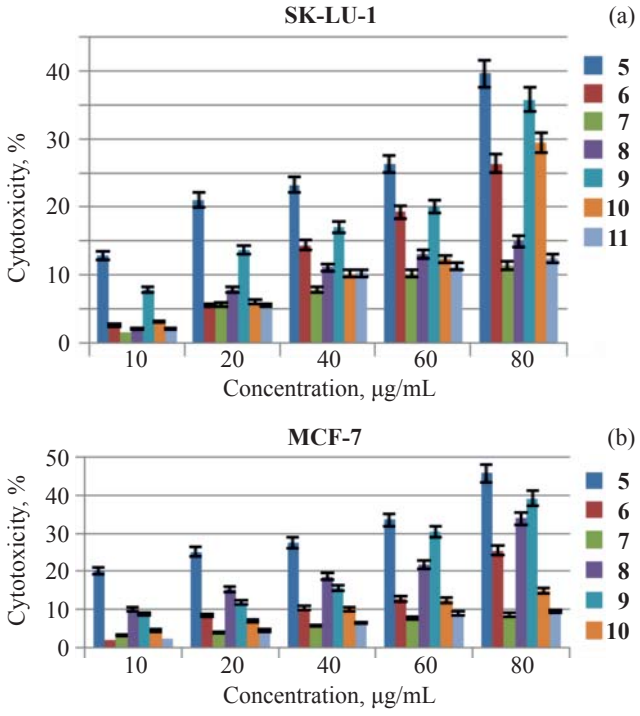


Fig. 1. Cytotoxicity of benzo[*f*]coumarin derivatives **5**–**11** against (a) SK-LU-1 and (b) MCF-7 cancer cell lines after exposure for 48 h.

EXPERIMENTAL

The melting points were measured on a Stuart SMP30 melting point apparatus (Switzerland) and are uncorrected. The IR spectra were recorded in KBr on a Shimadzu FT-IR 8201 PC spectrophotometer. The NMR spectra were obtained on a Varian Inova spectrometer at 500 MHz for ^{1}H and 125.65 MHz for ^{13}C with tetramethylsilane as internal standard. Analytical silica gel 60 F254 TLC plates were purchased from Merck. Elemental analyses (C, H, N) were carried out by using a Vario 3000 elemental analyzer (Shimadzu, Japan). All reagents were obtained from commercial suppliers and were used without further purification.

3-Acetyl-3*H*-benzo[*f*]chromen-3-one. Ethyl acetoacetate **2** (1.327 mg, 10.2 mmol) was added with stirring to a solution of 2-hydroxynaphthaldehyde **1** (1.722 mg, 10 mmol) in anhydrous ethanol (15 mL) containing a few drops of piperidine, and the mixture was stirred until a solid precipitated. The solid product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 93%, yellow crystals, mp 186–188°C, R_f 0.59. IR spectrum, ν, cm^{-1}: 3031, 2931 (C–H), 1735, 1681 (C=O), 1612, 1558, 1450 (C=C), 1211 (C–O). ^{1}H NMR spectrum (DMSO-d_6), δ,

ppm: 8.10 s (1H, 1-H), 7.89 d (1H, 5-H), 7.84 d (1H, 8-H), 7.68–7.04 m (4H, H_{arom}), 2.21 s (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 172.0 (2-C=O), 161.7 (C^3O), 155.5 (C^{10a}), 137.6 (C^1), 135.1–113.4, 29.5 (Me). Found, %: C 75.35; H 4.12. $C_{15}H_{10}O_3$. Calculated, %: C 75.62; H 4.23.

(*E*)-2-[3-(4-Hydroxyphenyl)prop-2-enoyl]-3*H*-benzo[*f*]chromen-3-one (4). A solution of compound **3** (1.191 mg, 5 mmol) and 4-hydroxybenzaldehyde (0.61 mg, 5 mmol) in ethanol was stirred at 50°C for 6 h in the presence of piperidine (TLC). After cooling, the mixture was stirred for 1 h at room temperature and left overnight, and the solid product was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 73%, brown crystals, mp 203–205°C, R_f 0.59. IR spectrum, ν, cm^{-1}: 3471 (O–H), 3078, 3031, 2985 (C–H), 1738, 1675 (C=O), 1604, 1558, 1458 (C=C), 1218, 1049 (C–O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.80 s (1H, OH), 8.42 s (1H, 1-H), 8.07 d (1H, 5-H), 8.04 d (1H, 8-H), 7.86 d (1H, $C_6H_4C\mathbf{H}$=), 7.68–6.76 m (8H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 171.1 (=CH**C**=O), 159.5 (C^3=O), 157.8 (C^{4a}), 149.1 (C^{10a}), 137.6 (C^1), 135.1–119.2 (C_{arom}). Found, %: C 77.56; H 4.29. $C_{22}H_{14}O_4$. Calculated, %: C 77.18; H 4.12.

Compounds 5–11 (*general procedure*). A mixture of the corresponding carboxylic acid (1 mmol), chalcone **4** (1 mmol), zinc chloride (1 mmol), and phosphoryl chloride (10 mL) was stirred at 65–70°C for 5–8 h. After completion of the reaction (TLC), the mixture was allowed to cool down to 25°C and poured onto crushed ice with stirring. The precipitate was collected by filtration, washed with cold water, dried, and recrystallized from an appropriate solvent.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 2-(3-chloro-2-methylanilino)pyridine-3-carboxylate (5). Yield 39 mg (65%), yellow powder, mp 236–238°C, R_f 0.55 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3313 (NH), 3062, 2977, 2931 (C–H), 1752, 1718, 1696 (C=O), 1643 (C=N), 1612, 1566 (C=C), 1542 (δNH), 1211, 1033 (C–O), 645 (C–Cl). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 10.25 br.s. (1H, NH), 8.35 s (1H, 1-H), 8.23 d (1H, 1H, 6′-H), 8.19 d (2H, 5-H, 8-H), 7.94 d (1H, 13-H), 7.92–6.67 m (14H, $H_{arom.}$), 2.28 s (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 174.5 (C^{11}), 165.0 (C^{15}), 162.5 ($C^{2'}$), 161.1 (C^3), 156.8 ($C^{6'}$), 155.0 (C^{10a}), 152.0 (C^{4a}), 150.0 (C^1), 146.0 (C^1), 145.0 (C^{13}), 143.9 ($C^{3'}$), 140.3 (C^2), 136.1–119.6 (C_{arom}), 18.3 (Me). Found, %: C 71.68; H 3.90; N 4.83. $C_{35}H_{23}ClN_2O_5$. Calculated, %: C 71.61; H 3.95; N 4.77.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 2-methyl-1-[(*Z*)-4-(methanesulfinyl)benzylidene]-1*H*-indene-3-carboxylate (6). Yield 68%, brown crystals, mp 212–214°C, R_f 0.63 (hexane–EtOAc, 7:3). IR spectrum, ν, cm^{-1}: 3055, 2931 (C–H), 1735, 1728, 1660 (C=O), 1626, 1566, 1542 (C=C), 1157, 1141, 1080 (C-O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.42 s (1H, 1-H), 8.19 d (1H, 6′-H), 8.06 d (1H, 5-H), 8.03 d (1H, 8-H), 7.86 d (1H, 13-H), 7.75–6.93 m (9H, $H_{arom.}$), 2.76 s (3H, SMe), 2.40 s (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 167.8 (C^{11}), 161.6 (C^{15}), 161.4 (C^3), 151.1 (C^{10a}), 149.1 (C^{4a}), 147.5 (C^1), 142.5 ($C^{2'}$), 141.9 (C^{4b}), 141.0 (C^{13}), 136.4 (C^{15}), 133.0–117.4 (C_{arom}), 41.1 (SMe), 13.2 (Me). Found, %: C 75.85; H 4.31. $C_{41}H_{28}O_6S$. Calculated, %: C 75.91; H 4.35.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 2-(2,3-dimethylanilino)-benzoate (7). Yield 74%, white crystals, mp 197–199°C, R_f 0.56 (hexane–EtOAc, 8:2). IR spectrum, ν, cm^{-1}: 3288 (NH), 3062, 2977, 2931 (C–H), 1732, 1715, 1665 (C=O), 1604, 1589 (C=C), 1527 (δNH), 1205, 1056 (C–O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 9.37 br.s (1H, NH), 8.48 s (1H, 1-H), 8.21 d (1H, 3b-H), 8.10 d (1H, 5-H), 8.09 d (1H, 8-H), 7.93 d (1H, 13-H), 7.91–7.05 m (14H, $H_{arom.}$), 2.31 s (3H, Me), 2.21 s (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 171.0 (C^{11}), 164.1 (C^{15}), 159.5 (C^3), 155.5 (C^{10a}), 149.2 (C^{4a}), 145.8 (C^{2b}), 145.0 (C^1), 137.6–114.5 (C_{arom}), 22.1 (Me), 18.5 (Me). Found, %: C 78.92; H 5.01; N 2.63. $C_{37}H_{27}NO_5$. Calculated, %: C 78.57; H 4.81; N 2.48.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoate (8). Yield 73%, yellow powder, mp 205–207°C, R_f 0.55 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3039, 2908 (C–H), 1738, 1721, 1668 (C=O), 1604, 1566 (C=C), 1172, 1085 (C–O), 987 (C–F). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.24 s (1H, 1-H), 8.13 d (1H, 5-H), 7.94 d (1H, 8-H), 7.89 d (1H, 13-H), 7.87–6.89 m (12H, H_{arom}), 3.54 t (1H, 16-H), 1.93 d (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 173.6 (C^{11}), 167.5 (C^{15}), 161.4 (C^3), 160.1 (C^{3b}), 153.6 (C^{10a}), 155.5, 149.9 (C^{4a}), 146.9 (C^1), 144.7 (C^{13}), 135.5–117.0 (C_{arom}), 49.9 (C^{16}), 14.6 (Me). Found, %: C 78.52; H 4.69. $C_{37}H_{25}FO_5$. Calculated, %: C 78.16; H 4.43.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-carboxylate (9). Yield 58%, white crystals, mp 229–232°C, R_f 0.47

(hexane–EtOAc, 8:2). IR spectrum, ν, cm^{-1}: 3055, 2931 (C–H), 1756, 1743, 1692, 1677 (C=O), 1604, 1566 (C=C), 1215, 1064, 1041 (C–O), 685 (C–Cl). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.61 s (1H, 1-H), 8.08 d (1H, 5-H), 8.02 d (1H, 8-H), 7.86 d (1H, 13-H), 7.76–6.67 (15H, H_{arom}), 3.50 s (3H, OMe), 2.19 s (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 175.0 (C^{11}), 164.7 (C^{16}), 160.3 (C^{15}), 159.9 (C^3), 155.6 ($C^{5'}$), 151.0 (C^{10a}), 147.9 (C^{4a}), 144.1 (C^1), 142.0 (C^{13}), 139.2 ($C^{2''}$), 134.0–116.1 (C_{arom}), 50.1 (OMe), 13.2 (Me). Found, %: C 71.25; H 3.74; N 2.19. $C_{40}H_{26}ClNO_7$. Calculated, %: C 71.91; H 3.92; N 2.10.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 2-(3-benzoylphenyl)-propanoate (10). Yield 63%, brown powder, mp 220–222°C, R_f 0.54 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3047, 2923 (C–H), 1733, 1724, 1704, 1665 (C=O), 1612, 1566 (C=C), 1164, 1020 (C–O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.49 s (1H, 1-H), 8.08 d (1H, 5-H), 8.05 d (1H, 8-H), 7.89 d (1H, 13-H), 7.85–7.04 m (14H, H_{arom}), 3.35–3.31 q (1H, 15-H), 1.39 d (3H, Me). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 177.9 (C^{18}), 170.0 (C^{11}), 168.1 (C^{15}), 155.5 (C^3), 154.5 (C^{10a}), 150.0 (C^{4a}), 148.0 (C^1), 144.0 (C^{13}), 140.0 (C^{1c}), 139.2 (C^{3b}), 138.5–115.7 (C_{arom}), 37.7 (C^{16}), 13.0 (Me). Found, %: C 78.32; H 4.15. $C_{38}H_{26}O_6$. Calculated, %: C 78.88; H 4.53.

4-[(1*E*)-3-Oxo-3-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)prop-1-en-1-yl]phenyl 3-(4,5-diphenyl-1,3-oxazol-2-yl)propanoate (11). Yield 49%, brown solid, mp 210–212°C, R_f 0.57 (hexane–EtOAc, 8:2). IR spectrum, ν, cm^{-1}: 3047, 2939 (C–H), 1740, 1720, 1664 (C=O), 1650 (C=N), 1604, 1542, 1488 (C=C), 1203, 1180, 1072 (C–O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 8.42 s (1H, 1-H), 8.17 d (1H, 5-H), 8.07 d (1H, 8-H), 7.91 d (1H, 13-H), 7.84–7.04 (9H, H_{arom}), 2.90–2.84 t (2H, 16-H), 2.73–2.69 t (2H, 15-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 174.1 (C^{11}), 167.6 (C^{15}), 163.5 (C^3), 156.8 ($C^{2'}$), 150.0 (C^{10a}), 149.9 (C^{4a}), 147.5 (C^1), 146.7 ($C^{5'}$), 144.9 (C^{13}), 141.7 ($C^{4'}$), 137.6–117.0 (C_{arom}), 30.7 ($CO\mathbf{C}H_2$), 26.5 ($2'$-CH_2). Found, %: C 77.13; H 4.09. $C_{40}H_{27}NO_6$. Calculated, %: C 77.78; H 4.41.

In vitro cytotoxicity assay. The cytotoxic activity of benzocoumarin derivatives against two human cancer cell lines (SK-LU-1, MCF-7) was evaluated using the MTT assay [25]. The cell cultures, 100 μL of 2×10^4 cells/mL in DMEM (Dulbecco's Modified Eagle's medium) containing 10% FBS (fetal bovine serum), were seeded in 96-well plates and incubated overnight at 37°C in 5% CO_2 atmosphere. Benzocoumarin derivatives **5**–**11**, were then added at concentrations of 10, 20, 40, 60, and 80 μM to 3 wells, and the plate was further incubated for 48 h. After replacing the old medium with fresh medium, an MTT solution (50 μL of 0.5 mg/mL in DMEM) was added to each well, and the plate was returned to incubator for another 4 h. The resulting formazan crystals were dissolved by adding 100 μL of DMSO to each well. The extent of MTT reduction within cells to formazan was calculated by measuring the absorbance at λ 570 nm on an ELISA microplate reader. The obtained data were used to calculate cell viability percentage (Fig. 1), and the IC_{50} values are given in Table 1.

Antimicrobial activity assay. Antimicrobial activity of the synthesized compounds was investigated in vitro against both Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*), as well as fungi (*Candida albicans*, *Aspergillus niger*) using the broth dilution method [26]. Preparation of nutrient broth, subculture, base layer medium, and agar medium was made according to the standard procedure. The standard and test compounds were dissolved in DMSO to obtain a concentration of 50 or 100 μg/mL. The samples were incubated at 37°C for 24 h (bacteria) or at 25°C for 7 days (fungi), and the inhibition zone diameter (mm) was measured (Table 2). Cephalexin and fluconazole were used as standard antibiotics to compare the results.

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CONFLICT OF INTEREST

The authors declared the absence of conflict of interest.

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