

Synthesis and anti-proliferative activity of novel oxepin-annulated coumarins

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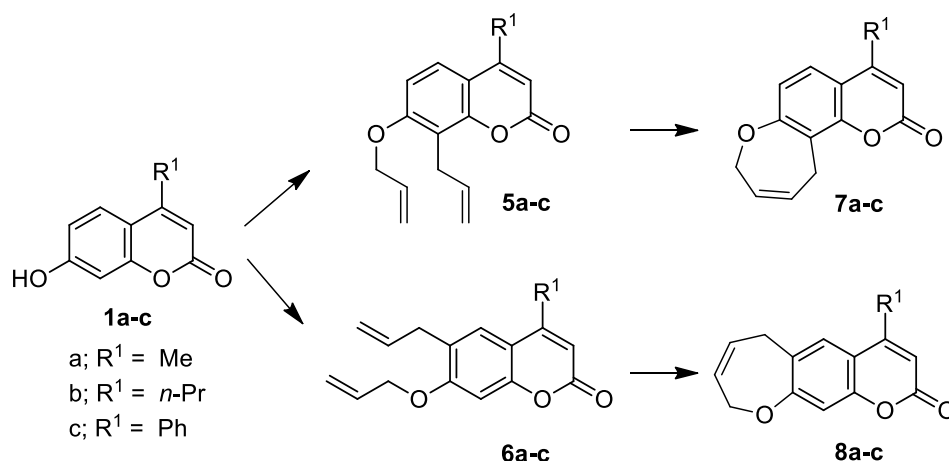
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Abstract

A series of fused dihydrooxepino[*h*]- and dihydrooxepino[*g*]coumarins (**7** and **8**) were synthesized through allylation, Claisen rearrangement, allylation and ring-closing metathesis (RCM), respectively. All the synthesized compounds were characterized by appropriate spectral analysis. The anti-proliferative activities of compound **5a-c**, **6a**, **6c**, **7a-c** and **8a-c** were evaluated against human colon cancer (Caco-2), liver cancer (HepG2) and breast cancer (SKBR-3) cell lines using tamoxifen (TAM) as the positive control. Compound **7b** showed significant anti-proliferative activity against resistant Caco-2 and SKBR-3 cell lines on comparison with all other coumarin derivatives. Interestingly, compound **8b** was more potent than TAM against sensitive HepG2 cell line.



Keywords: Claisen rearrangement, ring-closing metathesis, coumarin, oxepine, anti-proliferative activity

Introduction

Coumarins fused with 5- and 6-membered oxygen heterocycle, known as furocoumarins and pyranocoumarins, respectively, (Figure 1) are important structural units in many natural products and biologically active compounds. They exhibit a wide spectrum of pharmaceutical and biological properties, including anti-inflammatory,^{1,2} anti-HIV,³ anticancer,^{4,5} antioxidative,⁶ antifungal,⁷ antimicrobial,⁸ antibacterial,⁹ anticoagulant,¹⁰ anticonvulsant,¹¹ vasorelaxant¹² activities.

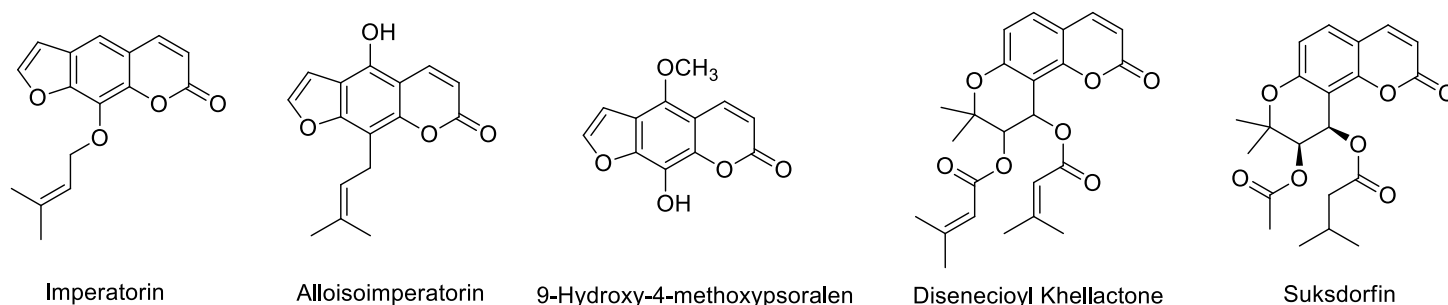


Figure 1. Examples of bioactive furocoumarins and pyranocoumarins.

Various natural products and bioactive compounds containing oxepane ring, 7-membered oxygen heterocycle,¹³⁻¹⁷ have been also reported with a broad range of interesting biological activities such as antidepressant,¹⁸ analgesic,¹⁹ antipsychotic,²⁰ antioxidant,²¹ antimycobacterial^{17,22} and anticancer^{23,24} (Figure 2).

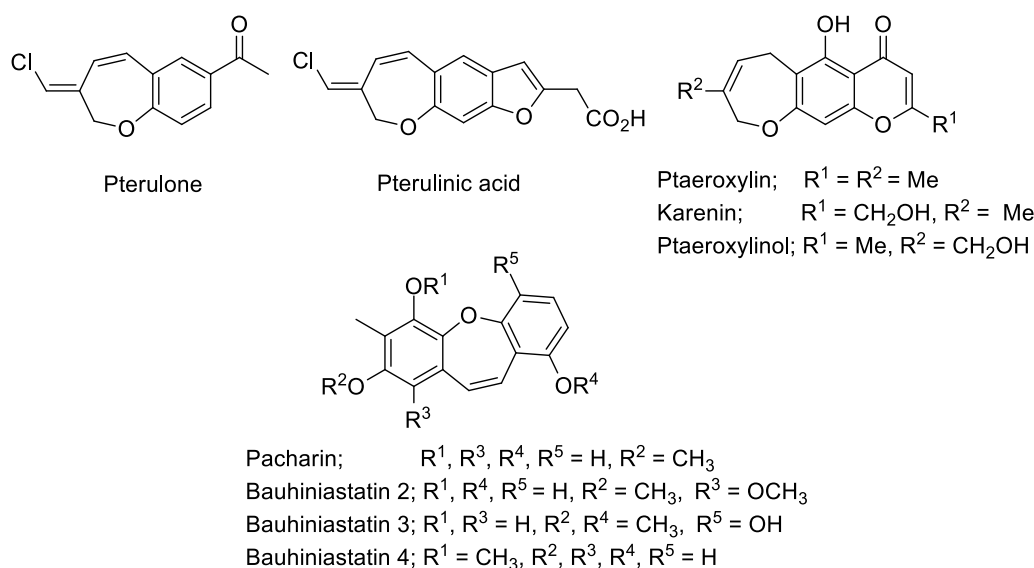


Figure 2. Examples of natural products and bioactive compounds containing 7-membered oxygen heterocycle.

Coumarins fused with heterocycles have gained much attention due to their potential biological activities. However, synthetic study and the evaluation for biological activities of medium ring oxacycle fused coumarins, especially oxepinocoumarins are scarce.^{25,26}

Among several methods for the construction of cyclic structures,²⁷⁻³² ring-closing metathesis (RCM) has proven to be a powerful method for the synthesis of carbocycles and heterocycles with various ring sizes.³³⁻³⁸

In continuation to our previous work on the synthesis of coumarin derivatives,³⁹ we wish to report here the synthesis of fused-dihydrooxepino[g]- and [h]coumarins through the combination of allylation, Claisen rearrangement, allylation and RCM, respectively. Moreover, the evaluation of anticancer activity of compounds **5a-c**, **6a**, **6c**, **7a-c** and **8a-c** against Caco-2, HepG2 and SKBR-3 cell lines was performed.

Result and Discussion

The synthesis of the target compounds **7** and **8** was carried out as described in Scheme 1. Coumarins (**1a-c**) were efficiently converted to the corresponding allyloxy coumarins (**2a-c**) in high yields (89-92%) by treatment with allyl bromide and K₂CO₃ under reflux in acetone for 16 h. The Claisen rearrangement of **2a-c** was carried out in ethylene glycol at 190°C in sand bath for 24 h leading to mixtures of respective regioisomers **3a-c** and **4a-c** in 45-96% combined yields.

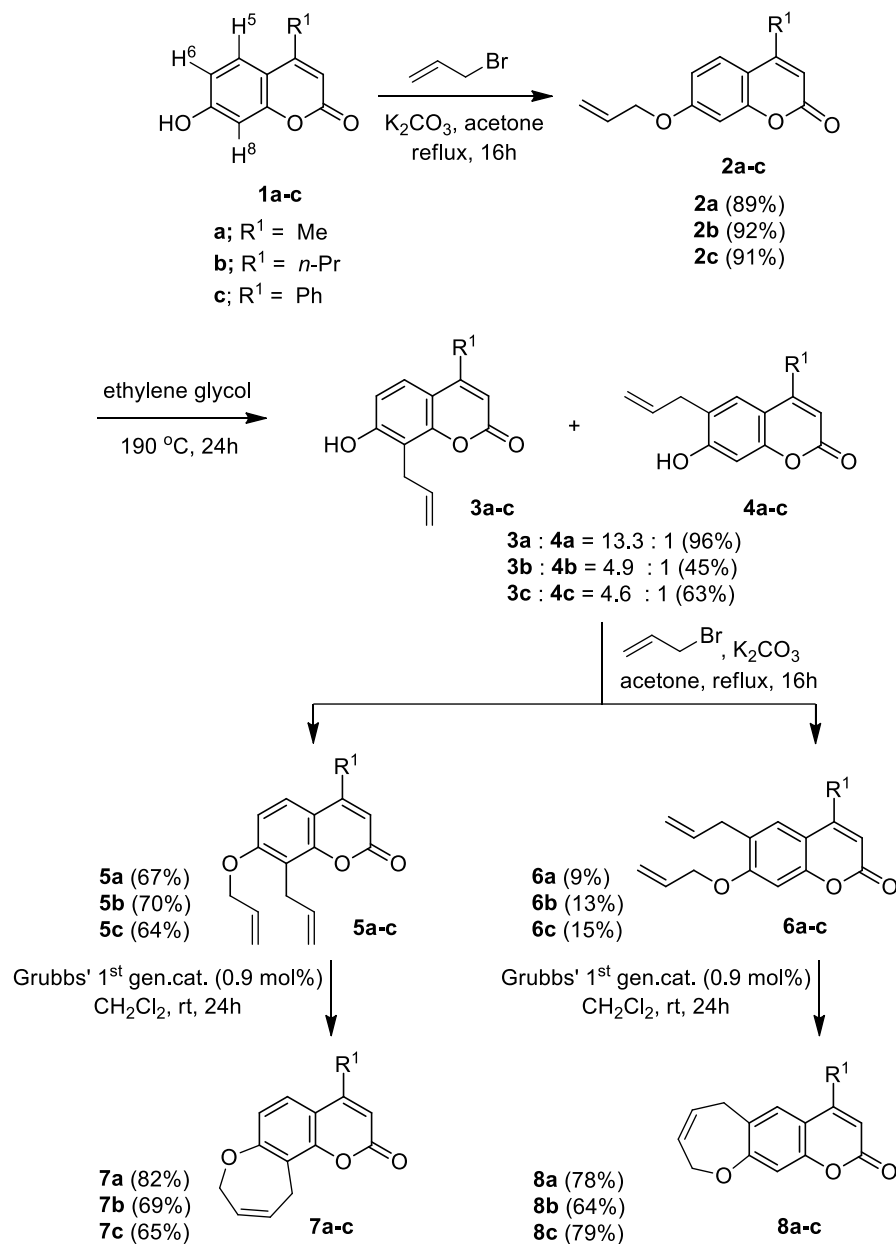
The ratios of two regioisomers **3** and **4** were determined by ¹H NMR spectra of pure mixtures by comparing the integration areas of H⁵ on the benzene rings of compounds **3** and **4**. ¹H NMR chemical shifts and splitting patterns of two protons on phenyl rings of **3** and **4** are listed on table 1. Because these two regioisomers were difficult to separate by standard chromatographic purification, we decided to use them as regioisomeric mixtures for the next allylation reaction.

Table 1. ¹H NMR (400 MHz, DMSO-*d*₆) of selected protons on benzene ring of compounds **3** and **4** and the calculated ratio of **3** and **4**

	δ of 3 (ppm)		δ of 4 (ppm)		Ratio of 3:4
	H ⁵	H ⁶	H ⁵	H ⁸	
a	7.50 (d, <i>J</i> 8.8 Hz)	6.89 (d, <i>J</i> 8.8 Hz)	7.43 (s)	6.75 (s)	13.3:1
b	7.52 (d, <i>J</i> 8.8 Hz)	6.86 (d, <i>J</i> 8.8 Hz)	7.44 (s)	6.73 (s)	4.8:1
c	7.13 (d, <i>J</i> 8.8 Hz)	6.82 (d, <i>J</i> 8.8 Hz)	7.08 (s)	6.82 (s)	4.5:1

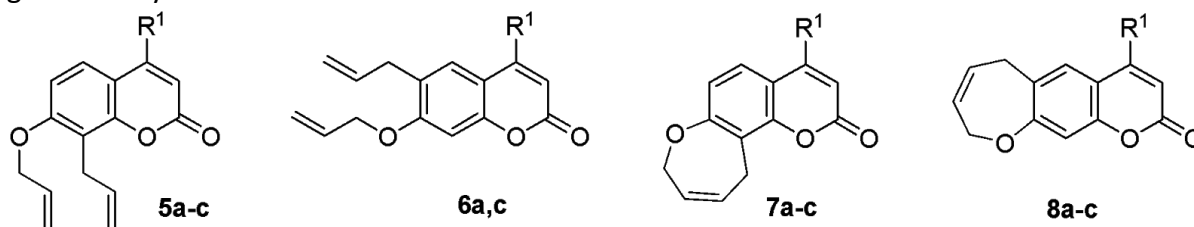
After completion of the allylation reaction and purification, compounds **5a-c** and **6a-c** were obtained as pure regioisomers in 64-70% and 9-15% yields, respectively. The RCM reactions of olefins **5a-c** and **6a-c** with Grubbs' first-generation catalyst in dichloromethane at room temperature for 24 h gave the expected metathesis products **7a-c** and **8a-c** in good yields (64-82%).

The synthesized compounds **5-8**, except for **6b**, were evaluated for their *in vitro* antiproliferative activity against three cancer cell lines including colorectal adenocarcinoma (Caco-2), hepatocellular carcinoma (HepG2) and breast carcinoma (SKBR-3) cell lines using MTT assay. The concentration-response studies were performed in order to determine their half-medium inhibitory concentration (IC₅₀) values (Table 2) by incubation of cell lines with 11 compounds at concentrations of 0-100 µg/mL for 48 h at 5% CO₂ and 37°C. Tamoxifen was also evaluated as references.



Scheme 1. Synthesis of fused dihydrooxepino[*h*]- and dihydrooxepino[*g*]coumarins (**7** and **8**).

From the analysis of Table 2, it can be concluded that compound **7b** was the most cytotoxic to Caco-2 and SKBR-3 cell lines with IC₅₀ of 30.05 ± 0.71 and 11.18 ± 1.93 µg/mL, respectively. It also showed potent activity on HepG2 cell with IC₅₀ values of 15.32 ± 0.30 µg/mL. Interestingly, compound **8b** has demonstrated the most promising activity against HepG2 cell line with IC₅₀ values of 8.78 ± 1.21 µg/mL, which is lower than that of tamoxifen, **5a** and **5b** (IC₅₀ values of 9.41 ± 1.81, 10.48 ± 3.44 and 10.42 ± 2.16 µg/mL, respectively). Comparison of the substitution at the C-4 position of the coumarin ring suggested that the propyl group contributed to the anti-proliferative activity enhancement. Compounds **5b**, **7b** and **8b** were more active than compounds **5a,c**, **7a,c** and **8a,c**, respectively against almost all tested cell lines. In addition, the nature of the angularly or linearly fused ring (**7** or **8**) did not significantly affect the activity. Among the tested cell lines, HepG2 has proven to be the most sensitive cell line. Approximately half of the tested coumarin derivatives presented high cytotoxicity (IC₅₀ ≤ 20 µg/mL). On the other hand, Caco-2 has proven to be the most resistant cell line, since almost all compounds exhibited moderate cytotoxicity (IC₅₀ ranged between 21 and 200 µg/mL).

Table 2. IC₅₀ values of coumarin derivatives **5-8** and tamoxifen against Caco-2, HepG2 and SKBR-3 cancer cell lines using MTT assay^a

a; R¹ = Me b; R¹ = *n*-Pr c; R¹ = Ph

Compound	IC ₅₀ (μg/mL)		
	Caco-2	HepG2	SKBR-3
5a	> 500	10.48 ± 3.44	38.80 ± 3.19
5b	105.22 ± 0.72	10.42 ± 2.16	165.61 ± 9.57
5c	49.10 ± 7.05	41.61 ± 3.49	59.70 ± 14.35
6a	> 500	59.04 ± 4.30	101.21 ± 20.23
6c	51.02 ± 24.11	21.05 ± 3.36	30.80 ± 1.42
7a	55.54 ± 21.18	18.64 ± 1.94	42.77 ± 2.43
7b	30.05 ± 0.71	15.32 ± 0.30	11.18 ± 1.93
7c	35.29 ± 1.24	37.77 ± 8.52	196.34 ± 2.03
8a	96.72 ± 9.15	24.3 ± 0.51	63.76 ± 17.67
8b	73.04 ± 7.82	8.78 ± 1.21	30.79 ± 8.50
8c	> 500	16.37 ± 2.27	28.33 ± 12.68
Tam	17.77 ± 2.79	9.41 ± 1.81	10.96 ± 1.85

^a Values represent mean ± standard deviation of three parallel measurements. The criteria used to categorize the cytotoxicity of coumarin derivatives against cancer cell lines, based on U.S. National Cancer Institute (NCI) and Geran protocol⁴⁰ were as follows: IC₅₀ ≤ 20 μg/mL = highly cytotoxic, IC₅₀ ranged between 21 and 200 μg/mL = moderately cytotoxic, IC₅₀ ranged between 201 and 500 μg/mL = weakly cytotoxic and IC₅₀ > 501 μg/mL = no cytotoxicity.

Conclusions

We have demonstrated a simple synthetic strategy for synthesis of fused-dihydrooxepino[g]- and [h]coumarins **7** and **8** via the allylation, Claisen rearrangement, allylation and RCM, respectively. The anti-proliferative activity of compound **5a-c**, **6a**, **6c**, **7a-c** and **8a-c** was screened against Caco-2, HepG2 and SKBR-3 cell lines using tamoxifen (TAM) as the positive control. Compound **7b** exhibited similar anti-proliferative activity against resistant SKBR-3 cell to TAM and demonstrated the most potent activity against Caco-2 among the tested coumarin derivatives. Compound **8b** displayed the most potent anti-proliferative activity against HepG2 cell line. Our results could be used as a starting point for development of powerful coumarin anticancer therapies.

Experimental Section

General. Melting points (°C) were measured with the Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer. Chemical shifts (δ) are given in ppm and refer to TMS or the residual undeuterated solvent as the internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, dd = double doublet, br.s = broad singlet. ESI mass spectra were recorded on a Thermo Finnigan LCQ Advantage Mass Spectrometer. High Resolution Mass Spectrometry was performed with a MicroTOFLC, Bruker Daltonics. FTIR spectra were obtained with a Perkin Elmer FT-IR Spectrum GX. Column chromatography was performed on silica gel (Kieselgel 60, 70-230 mesh, Merck) in common glass columns. Preparative TLC was carried out on silica gel plate (Merck silica gel 60 PF254). All chemicals were obtained from commercial suppliers, and were used without further purification. The required coumarin precursors **1a-c** were prepared via Pechmann reaction.³⁹

General procedure for allylation of 1a-c. To a solution of phenol derivative (**1**, 10 mmol) anhydrous K_2CO_3 (4.15 g, 30 mmol) in acetone (30 mL) was added allyl bromide (1.81 g, 15 mmol). The mixture was heated under reflux and stirring for 16-18 h. After cooling to room temperature, the precipitated solid was filtered and washed with acetone. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel using EtOAc/hexane as eluent to afford the corresponding allylic ether **2**.^{25,26}

7-(Allyloxy)-4-methyl-2H-chromen-2-one (2a). Yield 89%; white solid; mp 100-102 °C (from EtOAc-Hexanes) (lit⁴¹ mp 100-101 °C); R_f 0.68 (20% EtOAc/hexanes); IR (KBr): ν_{max} 3076, 3020, 2953, 1725, 1611, 1392, 1349, 1285, 1263, 1208, 1141, 1069, 994, 936, 857, 838, 810 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.49 (d, J 8.8 Hz, 1H), 6.88 (dd, J 8.8, 2.4 Hz, 1H), 6.83 (d, J 2.4 Hz, 1H), 6.14 (s, 1H), 6.11-5.94 (m, 1H), 5.44 (dd, J 17.2, 1.0 Hz, 1H), 5.34 (dd, J 10.6, 0.6 Hz, 1H), 4.60 (d, J 5.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.63 (C), 161.26 (C), 157.26 (C), 152.50 (C), 132.25 (CH), 125.54 (CH), 118.48 (CH_2), 113.74 (C), 112.81 (CH), 112.06 (CH), 101.82 (CH), 69.26 (CH_2), 18.63 (CH_3); MS (ESI⁺) m/z (%) 217.0 ($\text{M}+\text{H}^+$, 100).

7-(Allyloxy)-4-propyl-2H-chromen-2-one (2b).⁴² Yield 92%; light yellow oil; R_f 0.57 (20% EtOAc/hexanes); IR (nujol): ν_{max} 3082, 2963, 2934, 2875, 2402, 1732, 1614, 1557, 1510, 1456, 1392, 1277, 1201, 1146, 1100, 1012, 843, 580 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.51 (d, J 8.8 Hz, 1H), 6.86 (dd, J 8.6, 2.4 Hz, 1H), 6.81 (d, J 2.4 Hz, 1H), 6.10 (s, 1H), 6.10-5.95 (m, 1H), 5.43 (d, J 17.2 Hz, 1H), 5.32 (d, J 10.4 Hz, 1H), 4.59 (d, J 5.2 Hz, 2H), 2.69 (t, J 7.6 Hz, 2H), 1.71 (sext, J 7.6 Hz, 2H), 1.04 (t, J 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.45 (C), 161.35 (C), 156.14 (C), 155.50 (C), 132.27 (CH), 125.27 (CH), 118.33 (CH_2), 113.05 (C), 112.71 (CH), 110.92 (CH), 102.00 (CH), 69.21 (CH_2), 33.74 (CH_2), 21.46 (CH_2), 13.84 (CH_3); MS (ESI⁺) m/z (%) 245.5 ($\text{M}+\text{H}^+$, 100).

7-(Allyloxy)-4-phenyl-2H-chromen-2-one (2c). Yield 91%; white solid; mp 85-88 °C (from EtOAc-Hexanes) (lit⁴³ mp 85-87 °C); R_f 0.80 (40% EtOAc/hexanes); IR (neat): ν_{max} 3080, 1727, 1615, 1550, 1375, 1309, 1284, 1153, 1125, 1023, 938, 857, 777, 713 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.56-7.39 (m, 5H), 7.38 (d, J 9.2 Hz, 1H), 6.90 (d, J 2.4 Hz, 1H), 6.81 (dd, J 8.6, 2.4 Hz, 1H), 6.22 (s, 1H), 6.20-5.85 (m, 1H), 5.42 (dd, J 17.3, 1.4 Hz, 1H), 5.34 (dd, J 10.5, 1.3 Hz, 1H), 4.59 (d, J 5.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.74 (C), 161.18 (C), 155.94 (C), 155.79 (C), 135.58 (C), 132.16 (CH), 129.59 (CH), 128.83 (2CH), 128.38 (2CH), 127.99 (CH), 118.55 (CH_2), 112.81 (CH), 112.65 (C), 111.94 (CH), 102.02 (CH), 69.28 (CH_2); MS (ESI⁺) m/z (%) 279.2 ($\text{M}+\text{H}^+$, 100).

General procedure for Claisen rearrangement of 2a-c. A solution of allylic ether (**2**) (9 mmol) in ethylene glycol (45 mL) was heated under stirring at 190 °C in sand bath for 24 h. After cooling to room temperature, the mixture was quenched with water (50 mL) and the aqueous phase was extracted with EtOAc (3 x 45 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo and the residue

was purified by column chromatography on silica gel using EtOAc/hexane as eluent to give a mixture of regioisomers of **3** as a major product and **4** as a minor product. ^1H NMR and ^{13}C NMR were characterized only the major products.²⁶

8-Allyl-7-hydroxy-4-methyl-2H-chromen-2-one (3a) and 6-allyl-7-hydroxy-4-methyl-2H-chromen-2-one (4a). Yield 96% (**3a:4a** 93:7); pale yellow solid; mp 189-190 °C (from EtOAc-Hexanes); R_f (**3a**) 0.33, R_f (**4a**) 0.43 (33% EtOAc/hexanes); IR (KBr): ν_{max} 3220, 1688, 1606, 1566, 1387, 1318, 1049 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 10.46 (s, 1H), 7.50 (d, J 8.8 Hz, 1H), 6.89 (d, J 8.8 Hz, 1H), 6.13 (s, 1H), 6.09-5.80 (m, 1H), 5.05-4.96 (m, 2H), 3.45 (d, J 6.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 160.75 (C), 160.70 (C), 159.23 (C), 154.13 (C), 153.16 (C), 135.93 (CH), 124.33 (CH), 115.45 (CH₂), 113.33 (C), 112.53 (CH), 110.47 (CH), 26.97 (CH₂), 18.48 (CH₃); MS (ESI⁺) m/z (%) 217.5 (M+H⁺, 100).

8-Allyl-7-hydroxy-4-propyl-2H-chromen-2-one (3b) and 6-allyl-7-hydroxy-4-propyl-2H-chromen-2-one (4b). Yield 45% (**3b:4b** 83:17); light yellow solid; mp 191-203 °C (from EtOAc-Hexanes); R_f (**3b**) 0.30, R_f (**4b**) 0.23 (20% EtOAc/hexanes); IR (KBr): ν_{max} 3226, 2968, 1661, 1599, 1567, 1393, 1326, 1279, 1114, 915, 842, 805 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 10.42 (s, 1H), 7.52 (d, J 8.8 Hz, 1H), 6.86 (d, J 8.8 Hz, 1H), 6.05 (s, 1H), 6.12-5.83 (m, 1H), 5.07-4.89 (m, 2H), 3.43 (d, J 1.2 Hz, 2H), 2.68 (t, J 7.2 Hz, 2H), 1.61 (sext, J 7.6 Hz, 2H), 0.95 (t, J 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 160.88 (C), 159.10 (C), 157.63 (C), 153.38 (C), 135.90 (CH), 124.13 (CH), 116.14 (C), 115.52 (CH₂), 113.42 (CH), 112.55 (CH), 111.77 (CH), 109.53 (C), 33.43 (CH₂), 27.04 (CH₂), 21.93 (CH₂), 14.14 (CH₃); MS (ESI⁺) m/z (%) 245.2 (M+H⁺, 100).

8-Allyl-7-hydroxy-4-phenyl-2H-chromen-2-one (3c) and 6-allyl-7-hydroxy-4-phenyl-2H-chromen-2-one (4c). Yield 63% (**3c:4c** 82:18); light yellow solid; mp 188-190 °C (from EtOAc-Hexanes); R_f (**3c**) 0.33, R_f (**4c**) 0.20 (20% EtOAc/hexanes); IR (KBr): ν_{max} 3376, 3120, 2950, 1679, 1610, 1592, 1376, 1315, 1260, 1141, 1060, 995 cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 10.59 (s, 1H), 7.65-7.32 (m, 5H), 7.13 (d, J 8.8 Hz, 1H), 6.83 (d, J 8.8 Hz, 1H), 6.10 (s, 1H), 6.00-5.78 (m, 1H), 5.10-4.80 (m, 2H), 3.46 (d, J 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 160.60 (C), 159.49 (C), 156.34 (C), 153.75 (C), 135.90 (C), 135.78 (CH), 129.92 (CH), 128.87 (2CH), 128.81 (2CH), 126.08 (CH), 115.69 (CH₂), 113.78 (C), 112.78 (CH), 111.31 (C), 110.53 (CH), 27.09 (CH₂); MS (ESI⁺) m/z (%) 279.4 (M+H⁺, 100).

General procedure for allylation of the mixtures of 3a-c and 4a-c. The synthesis was carried out from the mixture of **3a-c** and **4a-c**, anhydrous K₂CO₃ and allyl bromide in acetone using the above general procedure for the synthesis of compounds **2a-c**. The diene products **5a-c** and **6a-c** were obtained after purification by column chromatography or preparative TLC using EtOAc/hexane as eluent.

8-Allyl-7-(allyloxy)-4-methyl-2H-chromen-2-one (5a). Yield 67%; light yellow solid; mp 85-86 °C (from EtOAc-Hexanes) [lit²⁵ mp 92-93 °C (from acetone)]; R_f 0.72 (33% EtOAc/hexanes); IR (KBr): ν_{max} 2965, 2924, 2855, 1716, 1605, 1385, 1278, 1123, 1056, 844, 813 cm^{-1} ; ^1H NMR (400 MHz, CDCl₃): δ 7.45 (d, J 8.8 Hz, 1H), 6.86 (d, J 8.8 Hz, 1H), 6.15 (s, 1H), 6.14-5.90 (m, 2H), 5.45 (dd, J 17.2, 1.6 Hz, 1H), 5.33 (dd, J 10.6, 1.4 Hz, 1H), 5.10 (dd, J 17.1, 1.7 Hz, 1H), 5.00 (dd, J 10.1, 1.6 Hz, 1H), 4.67 (d, J 4.8 Hz, 2H), 3.66 (d, J 6.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ 161.01 (C), 159.17 (C), 152.63 (C), 152.21 (C), 135.24 (CH), 132.70 (CH), 123.00 (CH), 117.54 (CH₂), 116.84 (C), 115.29 (CH₂), 114.15 (C), 112.24 (CH), 108.33 (CH), 69.42 (CH₂), 27.06 (CH₂), 18.46 (CH₃); MS (ESI⁺) m/z (%) 257.5 (M+H⁺, 100).

6-Allyl-7-(allyloxy)-4-methyl-2H-chromen-2-one (6a). Yield 9%; white solid; mp 103-104 °C (from EtOAc-Hexanes); R_f 0.63 (33% EtOAc/hexanes); IR (KBr): ν_{max} 3071, 2923, 1730, 1613, 1385, 1367, 1274, 1163, 1065, 991, 901, 880, 845 cm^{-1} ; ^1H NMR (400 MHz, CDCl₃): δ 7.34 (s, 1H), 6.80 (s, 1H), 6.14 (s, 1H), 6.12-5.92 (m, 2H), 5.47 (dd, J 17.2, 1.6 Hz, 1H), 5.35 (dd, J 10.6, 1.4 Hz, 1H), 5.18-5.06 (m, 2H), 4.63 (d, J 5.2 Hz, 2H), 3.46 (d, J 6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl₃): δ 161.34 (C), 159.24 (C), 153.96 (C), 152.51 (C), 136.09 (CH), 132.25 (CH), 125.94 (C), 124.96 (CH), 117.92 (CH₂), 116.13 (CH₂), 113.14 (C), 111.93 (CH), 99.89 (CH), 69.19

(CH₂), 34.00 (CH₂), 18.58 (CH₃); MS (ESI⁺) *m/z* (%) 257.5 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₆H₁₆NaO₃ [M+Na]⁺: 279.0997; found: 279.0995.

8-Allyl-7-(allyloxy)-4-propyl-2 H-chromen-2-one (5b). Yield 70%; white solid; mp 70-72 °C (from EtOAc-Hexanes); R_f 0.27 (5 % EtOAc/hexanes); IR (KBr): ν_{max} 3090, 3072, 2964, 2924, 2863, 1716, 1605, 1301, 1279, 1127, 1047, 913, 841 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.48 (d, *J* 8.8 Hz, 1H), 6.86 (d, *J* 8.8 Hz, 1H), 6.16 (s, 1H), 6.12-5.91 (m, 2H), 5.46 (dd, *J* 17.2, 1.2 Hz, 1H), 5.33 (dd, *J* 10.4, 1.2 Hz, 1H), 5.12 (dd, *J* 17.0, 1.4 Hz, 1H), 5.01 (dd, *J* 10.0, 0.8 Hz, 1H), 4.67 (d, *J* 4.8 Hz, 2H), 3.67 (d, *J* 6.4 Hz, 2H), 2.72 (t, *J* 7.6 Hz, 2H), 1.75 (sext, *J* 7.6 Hz, 2H), 1.07 (t, *J* 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.29 (C), 159.00 (C), 156.04 (C), 152.86 (C), 135.26 (CH), 132.72 (CH), 122.82 (CH), 117.54 (CH₂), 116.97 (C), 115.31 (CH₂), 113.48 (C), 111.15 (CH), 108.29 (CH), 69.40 (CH₂), 33.78 (CH₂), 27.11 (CH₂), 21.55 (CH₂), 13.82 (CH₃); MS (ESI⁺) *m/z* (%) 285.1 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₈H₂₀NaO₃ [M+Na]⁺: 307.1310; found: 307.1313.

6-Allyl-7-(allyloxy)-4-propyl-2H-chromen-2-one (6b). Yield 13%; light yellow solid; mp 60-62 °C (from EtOAc-Hexanes); R_f 0.20 (5% EtOAc/hexanes); IR (KBr): ν_{max} 3059, 2930, 1726, 1618, 1382, 1271, 1163, 1105, 986 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37 (s, 1H), 6.81 (s, 1H), 6.14 (s, 1H), 6.12-5.90 (m, 2H), 5.47 (dd, *J* 17.2, 1.2 Hz, 2H), 5.35 (dd, *J* 10.8, 1.2 Hz, 2H), 5.13 (s, 1H), 5.12-5.05 (m, 1H), 4.63 (d, *J* 5.2 Hz, 2H), 3.46 (d, *J* 6.4 Hz, 2H), 2.72 (t, *J* 7.6 Hz, 2H), 1.74 (sext, *J* 7.5 Hz, 2H), 1.07 (t, *J* 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.60 (C), 159.09 (C), 156.25 (C), 154.20 (C), 136.12 (CH), 132.27 (CH), 125.85 (C), 124.77 (CH), 117.92 (CH₂), 116.11 (CH₂), 112.50 (C), 110.81 (CH), 100.09 (CH), 69.18 (CH₂), 34.00 (CH₂), 33.70 (CH₂), 21.39 (CH₂), 13.86 (CH₃); MS (ESI⁺) *m/z* (%) 285.1 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₈H₂₀NaO₃ [M+Na]⁺: 307.1310; found: 307.1303.

8-Allyl-7-(allyloxy)-4-phenyl-2 H-chromen-2-one (5c). Yield 64%; white solid; mp 101-103 °C (from EtOAc-Hexanes); R_f 0.30 (10% EtOAc/hexanes); IR (KBr): ν_{max} 3084, 3061, 2926, 1716, 1605, 1558, 1424, 1374, 1277, 1118, 1069, 910, 861, 773, 700 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): μ 7.62-7.39 (m, 5H), 7.32 (d, *J* 8.8 Hz, 1H), 6.80 (d, *J* 8.8 Hz, 1H), 6.24 (s, 1H), 6.18-5.93 (m, 2H), 5.47 (dd, *J* 17.3, 1.3 Hz, 1H), 5.43 (dd, *J* 10.6, 1.0 Hz, 1H), 5.34 (dd, *J* 17.1, 1.4 Hz, 1H), 5.32 (dd, *J* 10.0, 1.1 Hz, 1H), 4.66 (d, *J* 5.0 Hz, 2H), 3.72 (d, *J* 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): μ 160.94 (C), 159.30 (C), 155.85 (C), 153.22 (C), 135.98 (C), 135.16 (CH), 132.64 (CH), 129.32 (CH), 128.67 (2CH), 128.37 (2CH), 125.71 (CH), 117.60 (CH₂), 117.04 (C), 115.42 (CH₂), 113.22 (C), 112.15 (CH), 108.34 (CH), 69.42 (CH₂), 27.14 (CH₂); MS (ESI⁺) *m/z* (%) 274.7 (23), 319.5 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₂₁H₁₈NaO₃ [M+Na]⁺: 341.1154; found: 341.1135.

6-Allyl-7-(allyloxy)-4-phenyl-2H-chromen-2-one (6c). Yield 15%; viscous liquid; R_f 0.23 (10% EtOAc/hexanes); IR (ATR): ν_{max} 3071, 2989, 2850, 1714, 1614, 1548, 1445, 1368, 1273, 1152, 992, 911, 852, 769, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): μ 7.60-7.34 (m, 5H), 7.23 (s, 1H), 6.86 (s, 1H), 6.21 (s, 1H), 6.12-5.99 (m, 1H), 5.99-5.81 (m, 1H), 5.46 (dd, *J* 17.2, 1.2 Hz, 1H), 5.34 (dd, *J* 10.8, 1.2 Hz, 1H), 5.01 (s, 1H), 5.00-4.90 (m, 1H), 4.64 (d, *J* 4.8 Hz, 2H), 3.35 (d, *J* 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): μ 161.11 (C), 159.48 (C), 155.70 (C), 154.75 (C), 136.01 (CH), 135.82 (C), 132.24 (CH), 129.43 (CH), 128.72 (2CH), 128.35 (2CH), 127.36 (CH), 126.09 (C), 117.93 (CH₂), 115.80 (CH₂), 112.11 (C), 111.99 (CH), 100.22 (CH), 69.29 (CH₂), 33.91 (CH₂); MS (ESI⁺) *m/z* (%) 274.2 (100), 305.3 (25), 318.6 (M⁺, 32); HRMS (MALDI-TOF): calcd for C₂₁H₁₈NaO₃ [M+Na]⁺: 341.1154; found: 341.1144.

General procedure for ring-closing metathesis of 5a-c and 6a-c. The solution of Grubbs' first-generation catalyst (4 mg, 0.9 mol%) in dry dichloromethane (DCM) (10 mL) was added to a solution of **5** or **6** (0.5 mmol) in dry DCM (40 mL) under N₂ atmosphere. The solution was stirred at room temperature for 24 h. After the evaporation of the solvent, the residue was separated by CC using EtOAc/hexane as eluent to give the oxepinocoumarins (**7** or **8**).^{25,26}

4-Methyl-8,11-dihydro-2H-oxepino[2,3-*h*]chromen-2-one (7a). Yield 82%; white solid; mp 118-120 °C (from EtOAc-Hexanes) [lit²⁶ mp 109-111 °C (from DCM)]; *R*_f 0.33 (20 % EtOAc/hexanes); IR (KBr): ν_{\max} 3082, 3025, 2979, 2927, 2837, 1727, 1708, 1598, 1425, 1385, 1270, 1077, 855 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.42 (d, *J* 8.6 Hz, 1H), 7.01 (d, *J* 8.6 Hz, 1H), 6.20 (d, *J* 1.2 Hz, 1H), 6.00-5.82 (m, 1H), 5.62-5.49 (m, 1H), 4.71-4.59 (m, 2H) 3.88-3.73 (m, 2H), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.03 (C), 160.69 (C), 152.38 (C), 151.09 (C), 127.30 (CH), 126.33 (CH), 123.32 (C), 123.16 (CH), 117.72 (CH), 116.33 (C), 113.08 (CH), 70.79 (CH₂), 22.49 (CH₂), 18.65 (CH₃); MS (ESI⁺) *m/z* (%) 229.1 (M+H⁺, 100).

4-Propyl-8,11-dihydro-2H-oxepino[2,3-*h*]chromen-2-one (7b). Yield 69%; light yellow solid; mp 85-87 °C (from EtOAc-Hexanes); *R*_f 0.53 (20 % EtOAc/hexanes); IR (KBr): ν_{\max} 2959, 2924, 2853, 1708, 1622, 1272, 1154, 1132, 1058, 1022, 842 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.46 (d, *J* 8.8 Hz, 1H), 7.00 (d, *J* 8.8 Hz, 1H), 6.19 (s, 1H), 6.01-5.82 (m, 1H), 5.68-5.49 (m, 1H), 4.71-4.59 (m, 2H) 3.88-3.71 (m, 2H), 2.72 (t, *J* 7.6 Hz, 2H), 1.73 (sext, *J* 7.6 Hz, 2H), 1.05 (t, *J* 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.85 (C), 160.97 (C), 156.20 (C), 151.32 (C), 127.30 (CH), 126.33 (CH), 123.49 (C), 122.98 (CH), 117.67 (CH), 115.68 (C), 112.00 (CH), 70.78 (CH₂), 33.93 (CH₂), 22.53 (CH₂), 21.52 (CH₂), 13.79 (CH₃); MS (ESI⁺) *m/z* (%) 257.0 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₆H₁₆NaO₃ [M+Na]⁺: 279.0997; found: 279.0990.

4-Phenyl-8,11-dihydro-2H-oxepino[2,3-*h*]chromen-2-one (7c). Yield 65%; white solid; mp 118-120 °C (from EtOAc-Hexanes); *R*_f 0.47 (20 % EtOAc/hexanes); IR (KBr): ν_{\max} 3070, 3028, 2924, 2854, 1723, 1597, 1370, 1260, 1073, 708 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.61-7.39 (m, 5H), 7.32 (d, *J* 8.6 Hz, 1H), 6.97 (d, *J* 8.6 Hz, 1H), 6.30 (s, 1H), 6.10-5.89 (m, 1H), 5.70-5.53 (m, 1H), 4.79-4.60 (m, 2H) 3.98-3.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 162.16 (C), 160.66 (C), 156.02 (C), 151.70 (C), 135.77 (C), 129.45 (CH), 128.75 (2CH), 128.36 (2CH), 127.34 (CH), 126.41 (CH), 125.86 (CH), 123.38 (C), 117.72 (CH), 115.43 (C), 113.06 (CH), 70.75 (CH₂), 22.56 (CH₂); MS (ESI⁺) *m/z* (%) 291.1 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₉H₁₄NaO₃ [M+Na]⁺: 313.0841; found: 313.0838.

4-Methyl-6,9-dihydro-2H-oxepino[3,2-*g*]chromen-2-one (8a). Yield 78%; white solid; mp 168-169 °C (from EtOAc-Hexanes); *R*_f 0.27 (20 % EtOAc/hexanes); IR (KBr): ν_{\max} 3055, 3024, 2928, 2850, 1709, 1611, 1389, 1362, 1151, 1135, 1067 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.32 (s, 1H), 7.05 (s, 1H), 6.22 (s, 1H), 6.00-5.85 (m, 1H), 5.61-5.47 (m, 1H), 4.73-4.60 (m, 2H) 3.57 (d, *J* 8.2 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.73 (C), 160.82 (C), 152.60 (C), 151.78 (C), 132.27 (C), 127.11 (CH), 126.02 (CH), 124.03 (CH), 116.04 (C), 113.69 (CH), 110.10 (CH), 71.40 (CH₂), 31.45 (CH₂), 18.49 (CH₃); MS (ESI⁺) *m/z* (%) 229.1 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₄H₁₂NaO₃ [M+Na]⁺: 251.0684; found: 251.0675.

4-Propyl-6,9-dihydro-2H-oxepino[3,2-*g*]chromen-2-one (8b). Yield 64%; white solid; mp 118-121 °C (from EtOAc-Hexanes); *R*_f 0.30 (30 % EtOAc/hexanes); IR (KBr): ν_{\max} 2960, 2926, 2853, 1708, 1621, 1154, 842 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.34 (s, 1H), 7.06 (s, 1H), 6.22 (s, 1H), 6.01-5.83 (m, 1H), 5.62-5.45 (m, 1H), 4.75-4.60 (m, 2H) 3.57 (d, *J* 3.2 Hz, 2H), 2.73 (t, *J* 7.6 Hz, 2H), 1.75 (sext, *J* 7.5 Hz, 2H), 1.08 (t, *J* 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.56 (C), 161.08 (C), 155.55 (C), 153.84 (C), 132.21 (C), 127.11 (CH), 126.02 (CH), 123.75 (CH), 115.39 (C), 112.58 (CH), 110.29 (CH), 71.41 (CH₂), 33.73 (CH₂), 31.52 (CH₂), 21.33 (CH₂), 13.79 (CH₃); MS (ESI⁺) *m/z* (%) 257.2 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₆H₁₆NaO₃ [M+Na]⁺: 279.0997; found: 279.0990.

4-Phenyl-6,9-dihydro-2H-oxepino[3,2-*g*]chromen-2-one (8c). Yield 79%; light yellow solid; mp 135-139 °C (from EtOAc-Hexanes); *R*_f 0.37 (20 % EtOAc/hexanes); IR (KBr): ν_{\max} 3061, 2927, 2855, 1725, 1615, 1378, 1359, 1275, 1146, 701 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.62-7.33 (m, 5H), 7.17 (s, 1H), 7.10 (s, 1H), 6.28 (s, 1H), 5.94-5.78 (m, 1H), 5.60-5.40 (m, 1H), 4.78-4.59 (m, 2H), 3.44 (d, *J* 3.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 161.93 (C), 160.76 (C), 155.34 (C), 154.24 (C), 135.63 (C), 132.21 (C), 129.50 (CH), 128.80 (2CH), 128.31 (2CH), 126.99 (CH), 126.42 (CH), 126.17 (CH), 115.04 (C), 113.73 (CH), 110.30 (CH), 71.36 (CH₂), 31.33 (CH₂); MS (ESI⁺) *m/z* (%) 274.2 (28), 291.2 (M+H⁺, 100); HRMS (MALDI-TOF): calcd for C₁₉H₁₄NaO₃ [M+Na]⁺: 313.0841; found: 313.0842.

Cell line maintenance. The Three cancer cell lines used in this study were obtained from ATCC (MD, USA) and are as follows: colorectal adenocarcinoma (Caco-2), hepatocellular carcinoma (HepG2) and breast carcinoma (SKBR-3) cell lines. The Caco-2 and HepG2 cells were cultured in EMEM medium whereas SKBR-3 was cultured in DMEM medium. All media (Gibco, Langley, VA, USA) were supplemented at 10% with fetal bovine serum (Gibco) and streptomycin plus penicillin (100 µg/mL and 100 U/mL, respectively; Sigma Co., Madrid, Spain). All cells were maintained at 37°C, 95% relative humidity with 5% CO₂ atmosphere.

Evaluation of cell viability. All the candidates oxepin-annulated coumarins **5-8** were evaluated *in vitro* for their anti-proliferative activity against three different cancer cell lines, colorectal adenocarcinoma (Caco-2), hepatocellular carcinoma (HepG2) and breast carcinoma (SKBR-3) cell lines using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay as previously reported technique.⁴⁴ In brief, cells were seeded into 96-well tissue culture plates in appropriated basal medium for each cell line containing 10% FBS to a final volume of 100 µL. The cells were subjected to different treatments after 24 h of seeding. The cells were then incubated for 48 h with test compounds, tamoxifen as a positive control, or vehicle (DMSO). MTT solutions were then added and cells were incubated for 3 h. After that, the supernatants were removed and the precipitated formazan was dissolved by adding 200 µL of DMSO. Absorbance at 570 nm was determined using a microplate reader (Varioskan™ Flash Multimode Reader; Thermo Scientific™). Results were calculated by subtracting blank readings.

Data analysis. The IC₅₀ values were obtained from the curve fitted to the means of the absorbance quotients with respect to the control.

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Supporting Information

Supporting Information associated with this article are available: ¹H and ¹³C spectra of compounds **2-8**.

References

1. Symeonidis, T.; Fylaktakidou, K.C.; Hadjipavlou-Litina, D.J.; Litinas, K.E. *Eur. J. Med. Chem.* **2009**, *44*, 5012. <https://doi.org/10.1016/j.ejmech.2009.09.004>
2. Lee, J.; Lee, Y.J.; Kim, J.; Bang, O.S. *Molecules* **2015**, *20*, 20967. <https://doi.org/10.3390/molecules201219738>
3. Olomola, T.O.; Mosebi, S.; Klein, R.; Traut-Johnstone, T.; Coates, J.; Hower, R.; Kaye, P.T. *Bioorg. Chem.* **2014**, *57*, 1. <https://doi.org/10.3390/molecules201219738>

4. Chauthé, S.K.; Mahajan, S.; Rachamalla, M.; Tikoo, K.; Singh, I.P. *Med. Chem. Res.* **2015**, *24*, 2476.
<https://doi.org/10.1007/s00044-014-1312-6>
5. Luo, K.W.; Sun, J.G.; Chan, J.Y.; Yang, L.; Wu, S.H.; Fung, K.P.; Liu, F.Y. *Chemotherapy* **2011**, *57*, 449.
<https://doi.org/10.1159/000331641>
6. Piao, X.L.; Park, I.H.; Baek, S.H.; Kim, H.Y.; Park, M.K.; Park, J.H. *J. Ethnopharmacol.* **2004**, *93*, 243.
<https://doi.org/10.1016/j.jep.2004.03.054>
7. Song, P.P.; Zhao, J.; Liu, Z.L.; Duan, Y.B.; Hou, Y.P.; Zhao, C.Q.; Wu, M.; Wei, M.; Wang, N.H.; Lv, Y.; Han, Z.J. *Pest Manag. Sci.* **2017**, *73*, 94.
<https://doi.org/10.1002/ps.4422>
8. Kaneria, A.R.; Giri, R.R.; Bhila, V.G.; Prajapati, H.J.; Brahmabhatt, D.I. *Arab. J. Chem.* **2017**, *10*, S1100.
<https://doi.org/10.1016/j.arabjc.2013.01.017>
9. Zhang, G.; Zhang, Y.; Yan, J.; Chen, R.; Wang, S.; Ma, Y.; Wang, R. *J. Org. Chem.* **2012**, *77*, 878.
<https://doi.org/10.1021/jo202020m>
10. Lipeeva, A.V.; Khvostov, M.V.; Baev, D.S.; Shakirov, M.M.; Tolstikova, T.G.; Shults, E.E. *Med. Chem.* **2016**, *12*, 674.
<https://doi.org/10.2174/1573406412666160129105115>
11. Tosun, F.; Kızılay, Ç.A.; Erol, K.; Kılıç, F.S.; Kürkçüoğlu, M.; Başer, K.H.C. *Food Chem.* **2008**, *107*, 990.
<https://doi.org/10.1016/j.foodchem.2007.08.085>
12. Wang, T.; Wang, C.; Zhou, N.; Pan, X.; He, H. *Med. Chem. Res.* **2015**, *24*, 2417.
<https://doi.org/10.1007/s00044-014-1303-7>
13. Macías, F.A.; Torres, A.; Galindo, J.L.G.; Varela, R.M.; Álvarez, J.A.; Molinillo, J.M.G. *Phytochemistry* **2002**, *61*, 687.
[https://doi.org/10.1016/S0031-9422\(02\)00370-9](https://doi.org/10.1016/S0031-9422(02)00370-9)
14. Bruder, M.; Haseler, P.L.; Muscarella, M.; Lewis, W.; Moody, C.J. *J. Org. Chem.* **2010**, *75*, 353.
<https://doi.org/10.1021/jo902117e>
15. Vyvyan, J.R.; Oaksmith, J.M.; Parks, B.W.; Peterson, E.M. *Tetrahedron Lett.* **2005**, *46*, 2457.
<https://doi.org/10.1016/j.tetlet.2005.02.053>
16. Zhang, C.L.; Liu, Y.F.; Wang, Y.; Liang, D.; Jiang, Z.B.; Li, L.; Hao, Z.Y.; Luo, H.; Shi, G.R.; Chen, R.Y.; Cao, Z.Y.; Yu, D.Q. *Org. Lett.* **2015**, *17*, 5686.
<https://doi.org/10.1021/acs.orglett.5b02982>
17. Li, H.; Jean, A.; Webster, D.; Robichaud, G.A.; Calhoun, L.A.; Johnson, J.A.; Gray, C.A. *J. Nat. Prod.* **2015**, *78*, 2837.
<https://doi.org/10.1021/acs.inatprod.5b00627>
18. Trabanco, A.A.; Alonso, J.M.; Andrés, J.I.; Cid, J.M.; Fernández, J.; Iturrino, L.; Megens, A. *Chem. Pharm. Bull.* **2004**, *52*, 262.
<https://doi.org/10.1248/cpb.52.262>
19. Agnew, M.N.; Rizwaniuk, A.; Ong, H.H.; Wichmann, J.K. *J. Heterocycl. Chem.* **1986**, *23*, 265.
<https://doi.org/10.1002/jhet.5570230155>
20. Trabanco, A.A.; Alonso, J.M.; Cid, J.M.; Font, L.M.; Megens, A. *Farmaco* **2005**, *60*, 241.
<https://doi.org/10.1016/j.farmac.2004.12.008>
21. Jinno, S.; Okita, T. *Heterocycles* **1999**, *51*, 303.
<https://doi.org/10.3987/COM-98-8390>

22. Kittakoop, P.; Nopichai, S.; Thongon, N.; Charoenchai, P.; Thebtaranonth, Y. *Helv. Chim. Acta* **2004**, *87*, 175.
<https://doi.org/10.1002/hlca.200490006>
23. Pettit, G.R.; Numata, A.; Iwamoto, C.; Usami, Y.; Yamada, T.; Ohishi, H.; Cragg, G.M. *J. Nat. Prod.* **2006**, *69*, 323.
<https://doi.org/10.1021/np058075+>
24. Wang, L.; Xie, S.; Ma, L.; Chen, Y.; Lu W. *Bioorg. Med. Chem.* **2015**, *23*, 1950.
<https://doi.org/10.1016/j.bmc.2015.03.031>
25. Chattopadhyay, S.K.; Maity, S.; Panja, S. *Tetrahedron Lett.* **2002**, *43*, 7781.
[https://doi.org/10.1016/S0040-4039\(02\)01806-3](https://doi.org/10.1016/S0040-4039(02)01806-3)
26. Litinas, K.E.; Mangos, A.; Nikkou, T.E.; Hadjipavlou-Litina, D.J. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 805.
<https://doi.org/10.3109/14756366.2011.555944>
27. Yet, L. *Chem. Rev.* **2000**, *100*, 2963.
<https://doi.org/10.1021/cr990407q>
28. Elliott, M.C. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1291.
<https://doi.org/10.1039/a903885j>
29. Nandi, S.; Singha, R.; Ray, J.K. *Tetrahedron* **2015**, *71*, 669.
<https://doi.org/10.1016/j.tet.2014.12.016>
30. Das, S.N.; Chowdhury, A.; Tripathi, N.; Jana, P.K.; Mandal, S.B. *J. Org. Chem.* **2015**, *80*, 1136.
<https://doi.org/10.1021/jo502672x>
31. Yadav, D.B.; Taleli, L.; van der Westhuyzen, A.E.; Fernandes, M.A.; Dragoun, M.; Prokop, A.; Schmalz, H.-G.; de Koning, C.B.; van Otterlo, W.A.L. *Eur. J. Org. Chem.* **2015**, 5167.
<https://doi.org/10.1002/ejoc.201500573>
32. Wang, Y.; Chen, Y.; He, Q.; Xie, Y.; Yang, C. *Helv. Chim. Acta* **2013**, *96*, 296.
<https://doi.org/10.1002/hlca.201200116>
33. van Otterlo, W.A.L.; Ngidi, E.L.; Coyanis, E.M.; de Koning, C.B. *Tetrahedron Lett.* **2003**, *44*, 311.
[https://doi.org/10.1016/S0040-4039\(02\)02522-4](https://doi.org/10.1016/S0040-4039(02)02522-4)
34. Doveston, R.G.; Steendam, R.; Jones, S.; Taylor, R.J.K. *Org. Lett.*, **2012**, *14*, 1122.
<https://doi.org/10.1021/ol300039x>
35. Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490.
<https://doi.org/10.1002/anie.200500369>
36. Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S.K. *Org. Lett.*, **2010**, *12*, 2032.
<https://doi.org/10.1021/ol100511d>
37. Calder, E.D.D.; Sharif, S.A.I.; McGonagle, F.I.; Sutherland, A. *J. Org. Chem.* **2015**, *80*, 4683.
<https://doi.org/10.1021/acs.joc.5b00583>
38. Aderibigbe, B.A.; Green, I.R.; Mabank, T.; van Rensburg, M.J.; Morgans, G.L.; Fernandes, M.A.; Michael, J.P.; van Otterlo, W.A.L. *Tetrahedron* **2017**, *73*, 4671.
<https://doi.org/10.1016/j.tet.2017.06.039>
39. Prateetongkum, S.; Duangdee, N.; Thongyoo, P. *Arkivoc* **2015**, (v), 248.
<http://dx.doi.org/10.3998/ark.5550190.p008.947>
40. Geran, R.I.; Greenberg, N.H.; MacDonald, M.M.; Schumaker, A.M.; Abbott, B.J. *Cancer Chemother. Rep.* **3** **1972**, *3*, 59.
41. Kaufman, K.D. US 3 201 421, 1965.
42. Ahluwalia, V.K.; Tripathi, R.P. *J. Indian Chem. Soc.* **1984**, *61*, 1023.

43. Ahuja, M.; Bandopadhyay, M.; Seshadri, T.R. *Indian J. Chem.* **1974**, 12, 292.
44. Scudiero, D.A.; Shoemaker, R.H.; Paull, K.D.; Monks, A.; Tierney, S.; Nofziger, T.H.; Currens, M.J.; Seniff, D.; Boyd, M.R. *Cancer Res.* **1988**, 48, 4827.