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Paper

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Synthesis and anti-cancer activity of diverse oxa-carbocycle fused isoflavones using the olefin metathesis

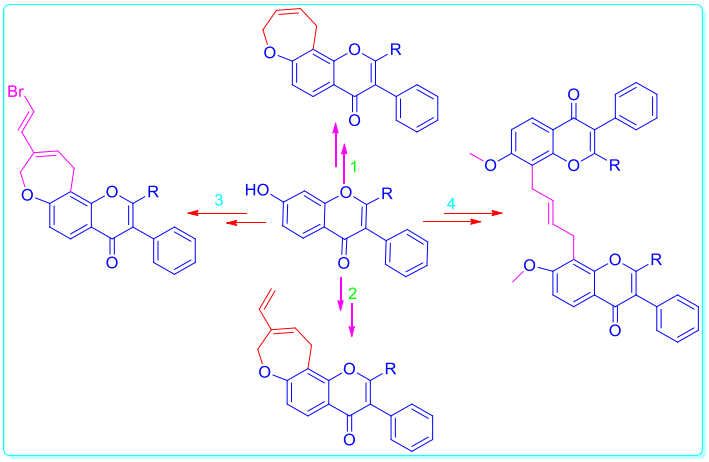
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Abstract

Isoflavones have been used as molecular scaffolds to design novel frameworks with desired pharmacological significance. An efficient and simple route for the synthesis of oxepine, annulated isoflavones and bis isoflavone skeletons has been developed by combined Claisen rearrangement, the ring-closing metathesis and cross metathesis. The synthesized compounds were tested against human cancer HeLa cell. Evolution of anti-cancer activity for all the synthesized compounds found to show good to moderate activity.



Keywords: Hydroxyisoflavones, Claisen rearrangement, ring-closing metathesis, Grubbs' I and II catalysts, oxa-carbocycle-annulated isoflavones, anti-cancer activity

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Introduction

Flavonoids are the most important polyphenolic family of secondary metabolites discovered in plants.[1] These compounds occur in vegetables, nuts, seeds, flowers and fruits[2-6] and are involved in a variety of biological processes.[2,4,7] Flavonoids have a wide range of qualities that are beneficial to human health by targeting with a wide range of cellular parts in the body's cell signalling pathways, which has provoked research into respective methods for the preparation of group targets. Some of the pharmacologically significant heterocyclic ring fused isoflavones are Osajin and Pomiferin[8] and Durmillone[9] isolated from the Millettia dura flowers. A number of methodologies have been reported in the literature for the synthesis of various heterocyclic ring fused isoflavones,[10,11] but medium size oxa-carbocycle annulated isoflavones are unknown, probably due to lack of general methods. The benzoxepines and benzoxocines are privileged structural scaffolds in medicinal chemistry because of their presence in several bioactive natural products such as pterulone**,** pterulinic acid,[12-14] ptaeroxylin, karenin, ptaeroxylinol [15-18] and heliannuols A-L.[19] The heliannuols are a group of phenolic allelochemicals isolated from the cultivar sun flowers *Helianthus annuus*. [20]

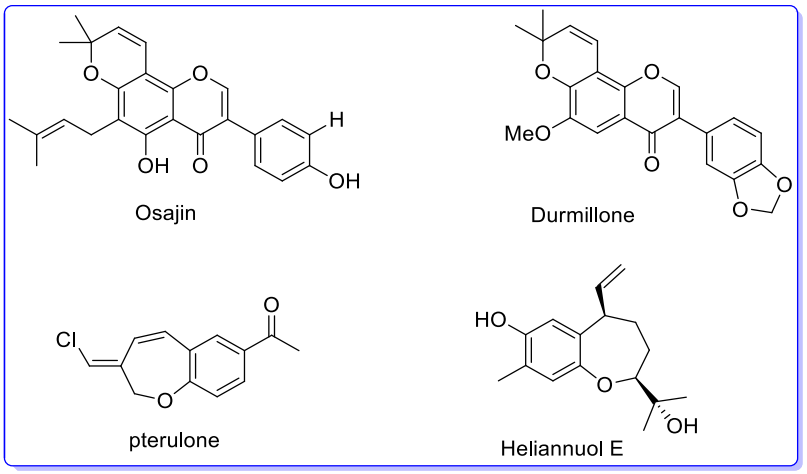


Figure 1. Some biologically active isoflavones and benzodiazepines.

The competing plant species eliminated or suppressed by allelochemicals near the plant source and are selective natural herbicides.[21,22] The structural features and wide range of biological activity of the heliannuols attracted organic chemists for the synthesis of these heterocycles fused to other bioactive heterocycles.

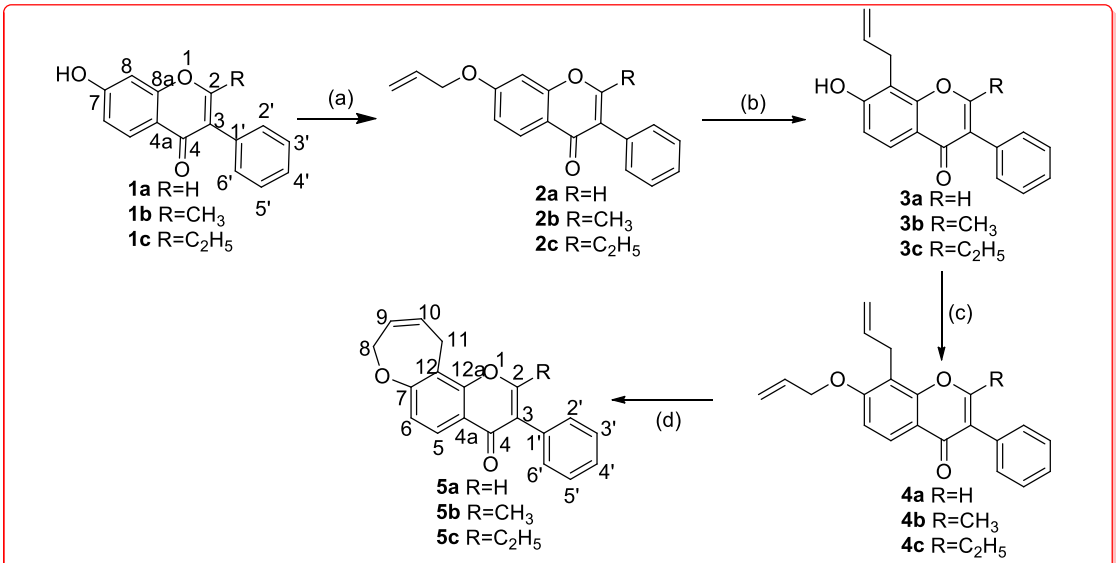
Ring-closing metathesis (RCM) using Grubbs' catalysts (I & II gen) is highly powerful and reliable tool to build the diverse carbocyclic and heterocyclic ring systems mainly for medium to large cyclics from diene and enyne precursors.[23-25] Moreover, till now there is no report of this tool being applied to develop angularly heterocycle ring annulation at isoflavones. We assumed that a sequence of the *Claisen* migration and RCM could be benefited to furnish diverse new oxa heterocycle-annulated isoflavone system of interest. Here we present a diversity-oriented strategy to construct the skeletally various oxa-carbocycle annulated isoflavone frame works through the application of sequential Claisen rearrangement and ring closing metathesis. Moreover, ring closer is a significant tool in the synthesis of natural products.

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Results and Discussion

The 7-Hydroxyisoflavone (**1a-c)** on treating with allyl bromide in acetone and K_2CO_3 yielded **2a-c.** Thermal Claisen rearrangement of **2a-c** in diphenyl ether under refluxing conditions, exclusively gave C-8 Regio isomer of **3a-c,**[26] which was already reported in solvent *N, N*-diethyl aniline, but we observed that diphenyl ether solvent was more practically suitable simpler than the previously published procedure.[26] The diene precursor of RCM **4a-c** were produced by alkylation with allyl bromide in refluxing acetone and K_2CO_3 medium from rearranged product **3a-c.** Several bioactive natural products such as *brevetoxins*[27] contain cyclic ethers. A strategic approach in the development of medium sized oxa-cycles is RCM. Treatment of the precursors **4a-c** with Grubbs' II catalyst (bis(tricyclohexyl phosphine) benzylidene ruthenium (IV) dichloride) (0.01M or 10 mol %) under refluxing in DCM for 1.5 hour resulted in the development of the desired **5a-c** in high yields (Scheme 1).

However, when the same reaction was carried out at room temperature with varied concentrations of Ru-catalyst, no conversion was observed. It is known that eight-membered cycloalkenes proved to reverse process, i.e., ring-opening metathesis (ROM), which is not observed in our synthetic route. In the ^{1}H-NMR spectra of **5a**, the characteristic signals of newly formed oxepino-ring protons resonated at δ 5.96 (m, 1H, H-10) 5.65 (m, 1H, H-9), 4.70 (d, *J* 3.8 Hz, 2H, H-8), 3.81 (d, *J* 3.4 Hz, 2H, H-11) were assigned to oxepine ring protons.

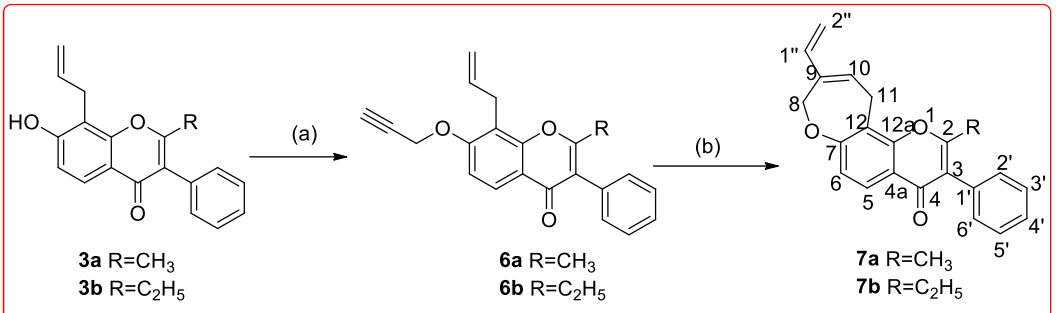


Scheme:1 a) Allyl bromide, K_2CO_3, acetone, reflux, 3h b) Diphenylether, refux, 3h c) Allyl bromide, K_2CO_3, acetone, reflux, 4h d) Grubbs'-II catalyst, CH_2Cl_2-reflux, 12h

We further moved to develop ene-yne metathesis in order to introduce vinyl group on oxepine ring which induce binding interaction with receptor. 8-allyl-7-hydroxy-3-phenyl-4*H*-chromen-4-ones (**3a-b)** was reacted with propargyl bromide in anhydrous K_2CO_3/acetone under reflux conditions yielding 8-allyl-3-phenyl-7-(prop-2-yn-1-yloxy) -4*H*-chromen-4-one **(6a-b)** (*Scheme-2*). Despite using several concentrations of Grubbs', I gen catalyst, no cyclized product of 3-phenyl-9-vinyl-8, 11-dihydro-4*H*-oxepino [2,3-*h*] chromen-4-ones **(7a-b)** was identified. As a result, another effort was made in CH_2Cl_2 under reflux conditions with Grubbs' II gen catalyst (10 mol %) for ring closure metathesis of 8-allyl-3-phenyl-7-(prop-2-yn-1-yloxy) -4*H*-chromen-4-ones **(6a-b)** which underwent ene-yne Ring closing metathesis and yielded 3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-

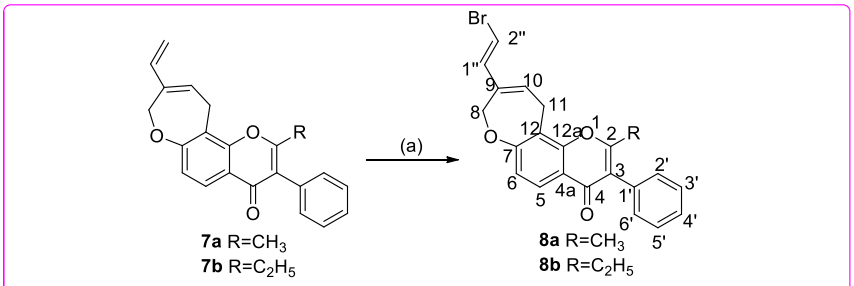
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h] chromen-4-ones **(7a-b)** (Scheme 2). ^{1}H NMR spectrum of **7a,** vinyl protons resonated at δ 5.13 (d, *J* 9.9 Hz, 2H, H-2''), 5.70 (t, *J* 6.8 Hz, 1H, H-1''). Oxepine ring protons resonated at δ 3.35 (s, 2H, H-8), 3.03 (d, *J* 6.8 Hz, 2H, H-11), 5.89 (t, *J* 9.9 Hz, 1H, H-10).



Scheme-2: a) Propargyl bromide, K_2CO_3, acetone, reflux, 4h b) Grubbs'-II catalyst, CH_2Cl_2-reflux, 12h

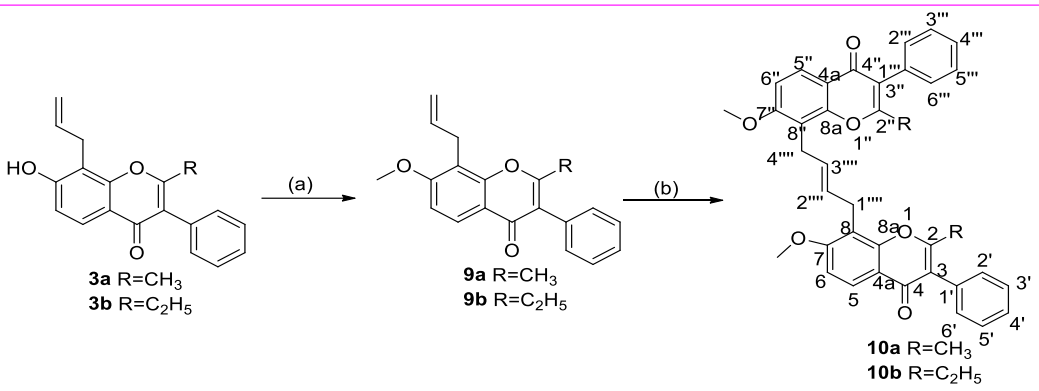
As halogen is a more electronegative atom and effectively involved in bond with targeted receptor, we focused our idea to develop (*E*)-9-(2-bromovinyl)-3-phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*] chromen-4-one **(8a-b)** by olefin metathesis of 3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*] chromen-4-ones **(7a-b)** and (*E*)-1,2-dibromoethene with Grubbs' I catalyst (0.01 M or 10 mol %, 3h) under reflux in CH_2Cl_2 provided exclusively angular oxepinone isoflavone derivatives, **8a-b** in quantitative yields (Scheme 3). The products were characterized by spectral data. In the ^{1}H NMR spectrum of **8a** vinyl protons resonated at 6.72 (d, *J* 14.7 Hz, 1H, H-2''), 6.53 (d, *J* 14.7 Hz, 1H, H-1''), oxepine protons appeared at δ 3.49 (s, 2H, H-8) 3.03 (d, *J* 6.8 Hz, 2H, H-11), 5.70 (t, *J* 6.8 Hz, 1H, H-10).



Scheme-3: a) (E)-1,2-dibromoethene, Grubbs'-**II** catalyst 3 mol%, CH_2Cl_2-reflux, 5h

Next, we focused our efforts on the synthesis of cross coupling reaction. 8-allyl-7-hydroxy-3-phenyl-4H-chromen-4-ones **(3a-b)** on treating with MeI in dry K_2CO_3/acetone at room temperature gave 8-allyl-7-methoxy-3-phenyl-4*H*-chromen-4-ones[28] (**9a-b)** (Scheme 4). The reaction of 8-allyl-7-methoxy-3-phenyl-4*H*-chromen-4-ones (**9a-b)** with **I** gen Grubbs' catalyst did not result in the formation of cross coupled products. When reacted with **II** gen Grubbs' catalyst (10mol %, 6h) under refluxing in DCM, the product **(***E***)**-8, 8'-(but-2-ene-1,4-diyl) bis(7-methoxy-3-phenyl-4H-chromen-4-one) (**10a-b)** was exclusively cross linked, with excellent yields (Scheme 4). In the ^{1}H NMR spectrum of **10a** two C-2, C-2'' methyl protons found at δ 1.92 (s, 6H, $2CH_3$) as a singlet. 7-OCH_3 protons appeared at δ 3.56 (s, 6H, $2OCH_3$). CH_2 protons appeared at δ 3.27 (d, *J* 6.4 Hz, 4H, H-1'''', H-4''''), olefinic protons observed at δ 5.77 (t, *J* 6.4 Hz, 2H, H-2'''', H-3'''')

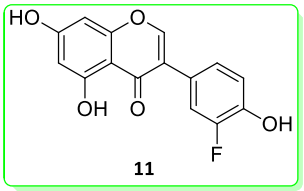
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Scheme-4: a) Methyl Iodide, K_2CO_3, acetone, reflux, 4h b) Grubbs'-II catalyst, CH_2Cl_2-reflux, 12h

Anti-Cancer Activity

The kinase activity is one more promising study of anticancer activity of compound **11**, recognized and characterized in the enzyme screen process.[28] Isoflavones have been used as useful molecular scaffolds to design novel frameworks with desired pharmacological significance.[29,30]



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Screening of anti-cancer activity was carried out for the isoflavone derivatives **(5a-c)**, **(7a-b)**, **(8a-b)**, **(10a-b)**. Cisplatin[6] was used as standard drug substances in the evaluation of biological activity for anti-cancer. Among the synthesized isoflavone derivatives **7a, 7b, 8a, 8b and 10a, 10b** compounds found to moderate anti-cancer agents with mean IC_{50} value of **94.1±1.4, 95.4±1.5, 64.5±0.1, 89.2±3.5, 80.1±0.5, 80.4±0.6** respectively.

Conclusions

We herein report an efficient and practical strategy for the synthesis of oxepine, angularly annulated and bisisoflavone and its related analogues by adopting combined Claisen rearrangement, the ring-closing metathesis and cross metathesis and disclosed some biological properties in relation with human cancer HeLa cell. Evolution of anti-cancer activity of synthesized compounds **5a-c, 7b-c, 8b-c** and **10b-c** against human cancer HeLa cell found to shown moderate activity with **IC_{50} (µM)** value ranged from **64.5±0.1 to 101.1±2.2.** The data reveal that the presence of a vinyl group, bromo vinyl group induce the anti-cancer activity.

Experimental Section

General. All reagents were purchased from Merck and other commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX operating at 400 MHz in $CDCl_3$ or DMSO-d_6 using TMS as the internal standard Melting points were determined (uncorrected) in open capillary tubes on a Buchi 530 melting point apparatus. TLC was performed to monitor progress of the reactions and

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assess purity of the compounds. Chromatograms were visualized under UV light. IR spectra (KBr) were recorded on an IRPrestige-21 Shimadzu spectrophotometer. Mass spectra were measured on a "Hewlett-Packard" HP GS/MS5890/5972. All solvents used were purified according to standard procedures.

7-Hydroxy-3-phenyl-4*H*-chromen-4-one (1a) was prepared by following the procedure given in the reference.[31] Yield 80%, Melting point 182-186 ^{o}C.

7-Hydroxy-2-methyl/ ethyl-3-phenyl-4*H*-chromen-4-ones (1b-c) was prepared by following the procedure given in the reference.[32,33] Yield 85%, Melting point 185-189 ^{o}C.

7-(Allyloxy)-3-phenyl-4*H*-chromen-4-one (2a). To a stirred solution of 7-hydroxy-3-phenyl-4*H*-chromen-4-one (**1a)** (2.0 g, 7.1 mmol) in acetone, allyl bromide (1.03 g, 8.5 mmol) and anhydrous K_2CO_3 (1.93 g, 14.2 mmol) were added and refluxed for 6 hours. acetone was evaporated and crude was diluted with ice cold water, the solid was separated by filtration, washed with water followed by pet-ether, and then dried to get 7-(allyloxy)-3-phenyl-4*H*-chromen-4-one (**2a)** as off-white solid in 84% yield.

8-Allyl-7-hydroxy-3-phenyl-4*H*-chromen-4-ones (3a). 7-(Allyloxy)-3-phenyl-4*H*-chromen-4-one (**2a**) (2.0 g, 6.7 mmol) was agitated at 185^{o}C for 3 hours and then cooled to room temperature in diphenyl ether (30 mL). Crude product by purification yielded 8-allyl-7-hydroxy-3-phenyl-4*H*-chromen-4-one (**3a**) as off-white solid.

8-Allyl-7-(allyloxy)-3-phenyl-4*H*-chromen-4-one (4a-c). At room temperature, K_2CO_3 (anhydrous) (0.82 g, 6.2 mmol) and allyl bromide (0.62 g, 5.1 mmol) were added to an 8-allyl-7-hydroxy-3-phenyl-4H-chromen-4-one **(3a)** solution in acetone (3.1 mmol). For 8 hours, the solution components were kept at a low temperature and the acetone evaporated. Ice-cold water was added. The precipitate was filtered and purified to give 8-allyl-7-(allyloxy) -3-phenyl-4*H*-chromen-4-one **(4a)** as off-white solid.

8-Allyl-7-(allyloxy) -3-phenyl-4*H*-chromen-4-one (4a). Off-white solid ; Yield : (86%) ; mp 99-101 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1629 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 8.41 (s, 1H, H_2), 7.61 (d, 1H, *J* 8.4 Hz, H_5), 7.48 (d, 2H, *J* 7.8 Hz, Ar-H), 7.28 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.21 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 5.83 (tt, 1H, *J* 13.8, 6.3 Hz, H-2'''), 5.63 (tt, 1H, *J* 13.8, 8.0 Hz, $H_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 5.18 (d, 2H, *J* 13.8 Hz, $H_{3'''}$), 3.79 (d, 2H, *J* 6.3 Hz, $H_{1'''}$), 3.07 (t, 2H, *J* 8.0 Hz, $H_{1''}$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 176.1 (C_4), 156.1 (C_7), 153.4 (C_{8a}), 153.3 (C_2), 136.0 ($C_{2''}$), 133.7 ($C_{2'''}$), 130.2 ($C_{1'}$), 128.7 ($C_{2'}$, $C_{6'}$), 128.5 ($C_{3'}$,$C_{5'}$), 126.1 (C_5), 125.5 (C_4), 124.7 (C_3), 120.2 (C_{4a}), 118.6 (C_6), 118.3 ($C_{3'''}$), 116.0 ($C_{3''}$), 113.4 (C_8), 68.9 (OCH_2), 31.4 (CH_2). HRMS (ESI) (*m/z*), [M+H]$^+$ calcd. For $C_{21}H_{18}O_3$: found : 319.13

8-Allyl-7-(allyloxy) -2-methyl-3-phenyl-4*H*-chromen-4-one(4b). White puffy solid ; Yield : (86%) ; mp 110-112 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1628 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 5.83 (tt, 1H, *J* 13.8, 6.3 Hz, $H_{2'''}$), 5.63 (tt, 1H, *J* 13.8, 8.0 H_2, $H_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 5.18 (d, 2H, *J* 13.8 Hz, $H_{3'''}$), 3.79 (d, 2H, *J* 6.3 Hz, $H_{1'''}$), 3.07 (d, 2H, *J* 8.0 Hz, $H_{1''}$), 2.15 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 179.9 (C_4), 159.4 (C_7), 156.14 (C_{8a}), 153.3 (C_2), 136.0 ($C_{2''}$), 133.7 ($C_{2'''}$), 129.0 ($C_{1'}$), 129.8, ($C_{2'}$, $C_{6'}$), 128.8 ($C_{3'}$, $C_{5'}$), 128.4, (C_5), 126.8 (C_4), 123.0, (C_3), 118.7 (C_{4a}), 118.6 (C_6), 115.6, ($C_{3'''}$), 115.4 ($C_{3''}$), 113.4 (C_8), 68.9 (OCH_2), 31.4 (CH_2), 18.6 (CH_3). HRMS (ESI) (*m/z*), [M+H]$^+$ calcd. For $C_{22}H_{20}O_3$: 333.1485, found : 333.1492.

8-Allyl-7-(allyloxy) -2-ethyl-3-phenyl-4*H*-chromen-4-one(4c). White puffy solid ; mp 108-111 ^{o}C ; yield (85%) ; FT-IR (KBr cm^{-1}) υ_{max} : 1631 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.28 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 5.83 (tt, 1H, *J* 13.8, 6.3 Hz, $H_{2'''}$), 5.63 (tt, 1H, *J* 13.8, 8.0 Hz, $H_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 5.18 (d, 2H, *J* 13.8 Hz, $H_{3'''}$), 3.79 (d, 2H, *J* 6.3 Hz, $H_{1'''}$), 3.07 (d, 2H, *J* 8.0 Hz, $H_{1''}$), 2.65 (q, 2H, *J* 7.8 Hz, CH_2), 1.25 (t, 3H, *J* 7.8 Hz, CH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 180.9 (C_4), 160.2 (C_7), 156.4 (C_{8a}), 153.2 (C_2), 136.0 ($C_{2''}$), 133.7 ($C_{2'''}$), 129.8 ($C_{1'}$), 128.8 ($C_{2'}$, $C_{6'}$), 128.5 ($C_{3'}$, $C_{5'}$), 128.2 (C_5), 124.8 (C_4), 121.7 ($C_{3'}$), 118.6 (C_{4a}), 118.3 (C_6), 115.6 ($C_{3''}$), 115.3 ($C_{5''}$),

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113.4 (C_8), 68.9 (OCH_2), 31.4 (CH_2), 24.9 (CH_2), 10.9 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calcd. For $C_{23}H_{22}O_3$: 347.1641, found: 347.1646.

3-Phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (5a-c). To a solution of the 8-allyl-7-(allyloxy)-3-phenyl-4H-chromen-4-one **(4a)** (100 mg, 0.3 mmol) in dry, degassed dichloromethane (8 mL) was added Grubbs' II gen catalyst (12 mg, 5 mol %) under intermedium(nitrogen) atmosphere and the observed resulting solution was subjected to stirring at ambient temperature for 1.5 hours. The dichloromethane (solvent) was evaporated in vacuo and the crude product was column chromatographed using 60-120 mesh and elution with 15% EtOAc-hexane to afforded pure **5a** as colourless solid.

3-Phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (5a). Colourless solid ; yield : (68%), mp 139-140 ^oC ; FT-IR (KBr, cm^{-1}) υ_{max} : 1628 (C=O). ^1H NMR (400 MHz, DMSO-d_6, δppm) : 8.17 (d, 1H, *J* 8.3 Hz, H_5). 8.03 (s, 1H, H_2), 7.57 (m, 2H, Ar-H) 7.45 (t, 2H, *J* 7.2 Hz, Ar-H) 7.39 (m, 1H, Ar-H) 7.13 (d, 1H, *J* 9.0 Hz, H_6), 5.96 (m, 1H, H_{10}) 5.65 (m, 1H, H_9), 4.70 (d, 2H, *J* 3.8 Hz, H_8), 3.81 (q, 2H, *J* 2.3 Hz, H_{11}). ^{13}C NMR (101 MHz, DMSO-d_6, δppm) : 176.1 (C_4), 163.1 (C_7), 153.8 (C_{12a}), 152.8 (C_2), 131.9 (C_9), 129.0 (C_{10}), 128.5 ($C_{2'}$, $C_{6'}$), 128.2 ($C_{3'}$, $C_{5'}$), 127.9 ($C_{4'}$), 125.9 (C_5), 125.7 ($C_{1'}$), 124.9 (C_3), 123.3 (C_{12}), 121.1 (C_{4a}), 119.7 (C_6), 70.5 (C_8), 22.5 (C_{11}). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{19}H_{14}O_3$: 291.1015, found : 291.1021.

2-Methyl-3-phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (5b). White solid ; yield : (74%) ; mp 134-138 ^oC ; FT-IR (KBr, cm^{-1}) υ_{max} : 1631 (C=O). ^1H NMR (400 MHz, DMSO-d_6, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.53 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* 8.4 Hz, H_6), 5.82 (dt, 1H, *J* 8.0, 4.6 Hz, H_{10}), 5.62 (m, 1H, H_9), 2.99 (d, 2H, *J* 4.6 Hz, H_8), 2.98 (d, 2H, *J* 6.4 Hz, H_{11}), 2.15 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δppm) : 181.7 (C_4), 160.2 (C_7), 153.9 (C_{12a}), 153.3 (C_2), 129.8 (C_{10}), 129.0 ($C_{2'}$, $C_{6'}$), 128.8 ($C_{3'}$, $C_{5'}$), 128.5 ($C_{4'}$), 128.0 (C_5), 126.5 ($C_{1'}$), 125.7 (C_3), 123.7 (C_{12}), 118.8 (C_{4a}), 109.7 (C_6), 66.0 (C_8), 35.4 (C_{11}), 18.6 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calcd. For $C_{20}H_{16}O_3$: 305.1172, found : 305.1175.

2-Ethyl-3-phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (5c). White solid ; yield : (74%) ; mp 137-139^oC. FT-IR (KBr, cm^{-1}) υ_{max} : 1635 (C=O). ^1H NMR (400 MHz, DMSO-d_6, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.53 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H) 7.17 (d, 1H, *J* 8.4 Hz, H_6), 5.82 (dt, 1H, *J* 8.0, 4.6 Hz, H_{10}), 5.62 (m, 1H, H_9), 2.99 (d, 2H, *J* 4.6 Hz, H_8), 2.98 (d, 2H, *J* 6.4 Hz, H_{11}), 2.68 (q, 2H, *J* 7.8 Hz, CH_2), 1.25 (t, 3H, *J* 7.8 Hz, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δppm): 182.5 (C_4), 160.0 (C_7), 153.9 (C_{12a}), 153.1 (C_2), 129.8 (C_{10}), 129.0 ($C_{2'}$, C6'), 128.8 ($C_{3'}$, $C_{5'}$), 128.5 ($C_{4'}$), 128.0 (C_5), 125.7 ($C_{1'}$), 125.3 (C_3), 124.0 (C_{12}), 118.7 (C_{4a}), 114.1 (C_{12a}), 111.2 (C), 66.0 (C), 35.4 (C_{11}), 24.9 (CH_2), 11.0 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{21}H_{18}O_3$: 319.1328, found : 319.1322.

Synthesis of 8-allyl-2-methyl-3-phenyl-7-(prop-2-yn-1-yloxy)-4H-chromen-4-one (6a-b). To the solution of 8-allyl-2-methyl-7-hydroxy-3-phenyl-4H-chromen-4-one **(3b)** (200 mg, 0.67 mmol) in dimethyl ketone (acetone) was added K_2CO_3 (anhydrous) (186 mg, 1.35 mmol) and alkynyl bromide (propargyl bromide) (97 mg, 0.81 mmol) at room temperature. The reaction mixture was refluxed for about 6h and acetone was removed, ice-cold water was added. Reaction was monitored by TLC. The precipitate was filtered and purified to give 8-allyl-2-methyl-3-phenyl-7-(prop-2-yn-1-yloxy) -4H-chromen-4-one (**6a)** as off-white solid.

8-Allyl-2-methyl-3-phenyl-7-(prop-2-yn-1-yloxy)-4*H*-chromen-4-one (6a). Off white solid ; Yield : (82%) ; mp 146-148 ^oC ; FT-IR (KBr, cm^{-1}) υ_{max} : 1695 (C=O). ^1H NMR (400 MHz, DMSO-d_6, δppm): 7.61 (d, *J* 8.4 Hz, 1H, H_5), 7.48 (d, *J* 7.8 Hz, 2H, Ar-H), 7.28 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.21 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 6.70 (s, 1H, $H_{2''}$), 5.63 (tt, 1H, *J* 13.8, 8.0 Hz, $H_{3'''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 4.76 (s, 1H, $H_{1'''}$), 3.07 (d, 2H, *J* 8.0 Hz, $H_{1''}$), 2.10 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6, δppm): 181.0 (C_4), 160.2 (C_7), 156.6 (C_{8a}), 152.0 (C_2), 136.3 ($C_{2''}$), 129.8 ($C_{1'}$), 129.0 ($C_{2'}$, $C_{6'}$), 128.8 ($C_{3'}$, $C_{5'}$), 128.5 ($C_{4'}$), 126.2 (C_5), 123.0 (C_6), 118.7(C_8), 116.5 (C_{4a}), 115.1 ($C_{3''}$), 113.6 (C_3), 87.2 ($C_{3'''}$), 82.9 ($C_{2'''}$), 59.2 ($C_{1'''}$), 28.6 (CH_2), 18.6 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{21}H_{16}O_3$: 317.1172, found : 317.1179.

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8-Allyl-2-ethyl-3-phenyl-7-(prop-2-yn-1-yloxy)-4*H*-chromen-4-one (6b). White puffy solid ; Yield : (82%) ; mp 151-153 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1692 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H$_5$), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H$_6$), 5.63 (tt, 1H, *J* 13.8, 8.0 Hz, H$_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, H$_{3''}$), 4.76 (s, 1H, H$_{3'''}$), 3.07 (d, 2H, *J* 8.0 Hz, H$_{1''}$), 2.65 (q, 2H, *J* 7.8 Hz, CH$_2$), 1.25 (t, 3H, *J* 7.8 Hz, CH$_3$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 184.6 (C$_4$), 160.2 (C$_7$), 156.6 (C$_{8a}$), 153.1 (C$_2$), 136.3 (C$_{2''}$), 129.8 (C$_{1'}$), 129.0 (C$_{2'}$, C$_{6'}$),128.8 (C$_{3'}$, C$_{5'}$), 128.4 (C$_5$), 126.8 (C$_{4'}$), 121.7 (C$_{4a}$), 118.7 (C$_8$), 115.6 (C$_{3''}$), 114.4 (C$_3$), 113.8 (C$_6$), 87.2 (C$_{2'''}$), 82.9 (C$_{3'''}$), 59.6 (C$_{1'''}$), 31.4 (C$_{1''}$), 24.9 (CH$_2$), 11.1 (C$_{2'}$). HRMS (ESI) (*m/z*), [M+H]$^+$ calculated. For $C_{22}H_{18}O_3$: 331.1328, found : 331.1324.

2-Methyl-3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (7a-b). To a solution of the substrate 8-allyl-2-methyl-3-phenyl-7-(prop-2-yn-1-yloxy)-4*H*-chromen-4-one **(6a)** (100 mg, 0.30 mmol) in dry, degassed CH_2Cl_2 (8 mL) was added Grubbs' II gen catalyst (24 mg, 10 mol %) under nitrogen atmosphere and the resulting solution was stirred at ambient temperature for 6 hours. Reaction was monitored by TLC. The solvent was evaporated in vacuo and the purification of the crude product was by column chromatography using 60-120 mash and Elution with 20% EtOAc/Pet-ether gave pure 2-methyl-3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*] chromen-4-one **(7a)** as colourless solid.

2-Methyl-3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (7a). Colourless solid ; Yield (46%) ; mp 68-69 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1695 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.51 (d, 1H, *J* 8.4 Hz, H$_5$), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.28 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* 8.4 Hz, H$_6$), 5.89 (t, 1H, *J* 9.9 Hz, H$_{10}$), 5.70 (t, 1H, *J* 6.8 Hz, H$_{1''}$), 5.13 (d, 2H, *J* 9.9 Hz, H$_{2''}$), 3.35 (s, 2H, H$_8$), 3.03 (d, *J* 6.8 Hz, 2H, H$_{11}$), 2.00 (s, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 179.9 (C$_4$), 159.4 (C$_7$), 155.6 (C$_{12a}$), 153.3 (C$_2$), 141.3 (C$_9$), 135.1 (C$_{1''}$), 130.1 (C$_{1'}$), 129.8 (C$_5$), 128.9 (C$_{2'}$, C$_{6'}$), 128.8 (C$_{3'}$, C$_{5'}$), 128.5 (C$_5$), 125.6 (C$_{4'}$), 123.0 (C$_3$), 118.7 (C$_{10}$), 115.7 (C$_{12}$), 114.1 (C$_{2'}$'), 111.2 (C$_6$), 65.6 (C$_8$), 34.1 (C$_{11}$), 18.6 (CH$_3$). HRMS (ESI) (*m/z*), [M+H]$^+$ calculated. For $C_{22}H_{18}O_3$: 331.1328, found : 331.1336.

2-Ethyl-3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (7b). Colourless solid ; Yield : (52%) ; mp 63-68 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1690 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.51 (d, 1H, *J* 8.4 Hz, H$_5$), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.28 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* 8.4 Hz, H$_6$), 5.89 (t, 1H, *J* 9.9 Hz, H$_{10}$), 5.70 (t, 1H, *J* 6.8 Hz, H$_{1''}$), 5.13 (d, 2H, *J* 9.9 Hz, H$_{2''}$), 3.35 (s, 2H, H$_8$), 3.03 (d, 2H, *J* 6.8 Hz, H$_1$), 2.65 (q, 2H, *J* 7.8 Hz, CH$_2$), 1.25 (t, 3H, *J* 7.8 Hz, CH$_3$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 182.4 (C$_4$), 160.2 (C$_7$), 156.6 (C$_2$), 153.1 (C$_{12a}$), 141.3 (C$_9$), 135.1 (C$_{1''}$), 130.1 (C$_{1'}$), 129.8 (C$_{2'}$, C$_{6'}$), 128.8 (C$_{3'}$, C$_{5'}$), 128.4 (C$_5$), 128.2 (C$_{4'}$), 126.1 (C$_3$), 121.7 (C$_{10}$), 118.3 (C$_{12}$), 115.7 (C$_{4a}$), 113.5 (C$_{2''}$), 111.2 (C$_6$), 65.6 (C$_8$), 34.1 (C$_{11}$), 24.9 (CH$_2$), 10.9 (CH$_3$). HRMS (ESI) (*m/z*), [M+H]$^+$ calculated. For $C_{22}H_{18}O_3$: 345.1485, found : 345.1493.

(*E*)-9-(2-Bromovinyl)-2-methyl-3-phenyl-8,11-dihydro-4*H*-oxepino[2,3-*h*] chromen-4-one (8a-b). Under argon atmosphere, Grubs-II gen catalyst (3 mol %) is added to a stirred solution of substituted 3-phenyl-9-vinyl-8,11-dihydro-4*H*-oxepino[2,3-*h*]chromen-4-one (s) **(7a-b)** (1.1 mmol) and 1,2 dibromo ethylene in anhydrous dichloromethane (15 mL). For 5 hours, the reaction mixture was stirred constantly and allowed to rt. After that, it was allowed to cool to ambient temperature before being concentrated in vacuo to produce a crude mass. The residue was refined further yielding (E)-9-(2-bromovinyl) -2-methyl-3-phenyl-8, 11-dihydro-4*H*-oxepino [2, 3-*h*] chromen-4-one **(8a-b)** as Colourless solid.

(*E*)-9-(2-bromovinyl)-2-methyl-3-phenyl-8,11-dihydro-4*H*-oxepino [2,3-*h*] chromen-4-one (8a). Colourless solid ; Yield : (56%) ; mp 67-70 ^{o}C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1701 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H$_5$), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.29 (dd, 3H, *J* 7.8, 7.5 Hz, Ar-H), 7.24 (t, 1H, *J* 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* 8.4 Hz, H$_6$), 6.72 (d, 1H, *J* 14.7 Hz, H$_{2''}$), 6.53 (d, 1H, *J* 14.7 Hz, H$_{1''}$), 5.70 (t, 1H, *J* 6.8 Hz, H$_{10}$), 3.49 (s, 2H, H$_8$) 3.03 (d, 2H, *J* 6.8 Hz, H$_{11}$) 2.10 (s, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 182.3 (C$_4$), 158.7 (C$_7$), 156.6 (C$_2$), 152.9 (C$_{12a}$), 133.6 (C$_9$), 130.5 (C$_{1''}$), 128.8 (C$_{1'}$) 128.4 (C$_{2'}$,C$_{6'}$), 128.2 (C$_{3'}$, C$_{5'}$), 128.0 (C$_5$),

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126.8 ($C_{4'}$), 126.4 (C_3), 122.0 (C_{10}), 121.3 (C_{12}), 116.2 (C_{4a}), 113.1 ($C_{2''}$), 111.7 (C_6), 66.3 (C_8), 34.1 (C_{11}), 19.0 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{22}H_{17}BrO_3$: 409.0433, found : 409.0427.

(*E*)-9-(2-Bromovinyl)-2-ethyl-3-phenyl-8,11-dihydro-4*H*-oxepino [2,3-*h*] chromen-4-one (8b). Colourless solid ; Yield : (58%) ; mp 65-72 °C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1702 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.29 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.28 (t, 2H, *J* 7.5 Hz, Ar-H), 7.16 (d, 1H, *J* 8.4 Hz, H_6), 6.72 (d, 1H, *J* 14.7 Hz), 6.53 (d, 1H, *J* 14.7 Hz, $H_{2''}$), 5.70 (t, 1H, *J* 6.8 Hz, $H_{1''}$), 3.49 (s, 2H, H_8), 2.94 (d, 2H, *J* 6.8 Hz, H_{11}), 2.65 (q, 2H, *J* 7.8 Hz, CH_2), 1.23 (t, 3H, *J* 7.8 Hz, CH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 185.5 (C_4), 156.7 (C_7), 156.6 (C_2), 153.1 (C_{12a}), 133.6 (C_9), 128.8 ($C_{1''}$), 128.6 ($C_{1'}$) 128.2 ($C_{2'}$, $C_{6'}$), 128.0 (C_5), 126.8 ($C_{3'}$, $C_{5'}$) 125.9 ($C_{4'}$), 122.0 (C_{10}), 119.2 (C_{4a}), 115.5 (C_{12}), 113.1 (C_3), 111.7 ($C_{2''}$, C_6), 67.1 (C_8), 33.0 (C_{11}), 24.9 (CH_2), 10.9 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{23}H_{19}BrO_3$: 423.0590, found : 423.0582.

8-Allyl-7-methoxy-2-methyl-3-phenyl-4*H*-chromen-4-one (9a-b). To a solution of 8-allyl-7-hydroxy-2-methyl-3-phenyl-4H-chromen-4-one **(3b)** (1 mmol) in 6 mL of dimethyl formamide (DMF), added dry K_2CO_3 (1.3 mmol) in DMF (2 mL) with continuous stirring. Later Iodomethane (75 µL, 0.11 mmol) was added and continued stirring for 5.5 hours at 65 °C. It was brought to room temperature by added water and the product was extracted into DCM (dichloromethane). The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The product was purified by liquid chromatography using hexane/EtOAc (60 :40) to afford pure 8-allyl-7-methoxy-2-methyl-3-phenyl-4*H*-chromen-4-one **(9a)** as off-white solid.

8-Allyl-7-methoxy-2-methyl-3-phenyl-4*H*-chromen-4-one (9a). Off-white solid ; Yield : (68%) ; mp 128-133 °C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1628 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.61 (d, 1H, *J* 8.4 Hz, H_5), 7.53 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (d, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 5.63 (tt, 1H, *J* 13.8 Hz, $H_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 3.43 (s, 3H, OCH_3), 3.07 (d, 2H, *J* 8.0 Hz, $H_{1''}$), 2.15 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm) : 181.8 (C_4), 160.2 (C_7), 157.3 (C_{8a}), 153.5 (C_2), 136.0 ($C_{2''}$), 129.8 ($C_{1'}$), 128.8 ($C_{2'}$, $C_{3'}$, $C_{5'}$, $C_{6'}$), 128.6 (C_5), 126.1 ($C_{4'}$), 118.8 (C_8), 116.5 (C_{4a}), 115.4 ($C_{3''}$), 109.3 (C_6), 55.7 (OCH_3), 28.6 ($C_{1''}$), 18.6 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{20}H_{18}O_3$: 307.1328, found : 307.1321.

2-Ethyl-7-methoxy-3-phenyl-8-(prop-2-en-1-yl)-4*H*-1-benzopyran-4-one (9b). White puffy solid ; Yield (54%) ; mp 152-159 °C (Lit.[90] 149-150 °C) ; FT-IR (KBr, cm^{-1}) υ_{max} : 1631 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.57 (d, 1H, *J* 8.4 Hz, H_5), 7.46 (d, 2H, *J* 7.8 Hz, Ar-H), 7.30 (dd, 2H, *J* 7.8, 7.5 Hz, Ar-H), 7.22 (t, 1H, *J* 7.5 Hz, Ar-H), 7.10 (d, 1H, *J* 8.4 Hz, H_6), 5.63 (tt, 1H, *J* 13.8 Hz, $H_{2''}$), 5.33 (d, 2H, *J* 13.8 Hz, $H_{3''}$), 3.43 (s, 3H, OCH_3), 3.07 (d, 2H, *J* 8.0 Hz, $H_{1''}$) 2.62 (q, 2H, *J* 7.8 Hz, CH_2) 1.25 (t, 3H, *J* 7.8 Hz, CH_3).^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 182.5 (C_4), 160.4 (C_7), 157.3 (C_{8a}), 153.2 (C_2), 136.0 ($C_{2''}$), 129.8 ($C_{1'}$), 129.0 ($C_{2'}$, $C_{6'}$), 128.8 ($C_{3'}$, $C_{5'}$), 128.5 (C_5), 126.1 ($C_{4'}$), 121.7 (C_3), 118.7 (C_{4a}), 116.0 ($C_{3''}$), 115.4 (C_6), 110.0 (C_8), 55.7 (OCH_3), 31.4 ($C_{1''}$), 24.9 (CH_2), 11.0 (CH_3). HRMS (ESI) (*m/z*), $[M+H]^+$ calculated. For $C_{21}H_{20}O_3$: 321.1485, found : 321.1492.

(*E*)-8,8'-(But-2-ene-1,4-diyl)bis(7-methoxy-3-phenyl-4*H*-chromen-4-one) (10a-b). A pear-shaped flask with a stir bar was charged with 8-allyl-7-methoxy-3-methyl-3-phenyl-4*H*-chromen-4-one (**8a)** (0.5 mmol), Grubbs-II gen catalyst (3 mol %), in dichloromethane as solvent under nitrogen inert atmosphere. The reaction was refluxed at 35°C with continued stirring for 10 hours. After cooling to room temperature, the reaction mixture was concentrated *in-vacuo* and the residue was purified by liquid chromatography, under the conditions noted, and afforded pure (E)-8, 8'-(but-2-ene-1,4-diyl) bis (7-methoxy-2-methyl-3-phenyl-4H-chromen-4- one) (**10a**) as off-white solid.

(*E*)-8,8'-(but-2-ene-1,4-diyl)bis(7-methoxy-2-methyl-3-phenyl-4*H*-chromen-4-one) (10a). Off-white solid ; Yield : (56%) ; mp 204-206 °C ; FT-IR (KBr, cm^{-1}) υ_{max} : 1632 (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$, δppm): 7.65 (d, 2H, *J* 8.4 Hz, H_5, $H_{5''}$), 7.42 (d, 4H, *J* 7.8 Hz, Ar-H), 7.41 (dd, 4H, *J* 7.8, 7.5 Hz, Ar-H), 7.33 (t, 2H, *J* 7.5 Hz, Ar- H), 7.10 (d, 2H, *J* 8.4 Hz, C_6, $C_{-6''}$), 5.77 (t, 2H, *J* 6.4 Hz, $H_{2''''}$, $H_{3''''}$), 3.56 (s, 6H, $2OCH_3$), 3.27 (d, 4H, *J* 6.4 Hz, $_{H1''''}$, $H_{4''''}$), 1.92 (s, 6H, $2CH_3$). ^{13}C NMR (101 MHz, DMSO-*d*$_6$, δppm): 185.4 (C_4, $C_{4''}$), 158.8 (C_7, $C_{7''}$), 155.2 (C_{8a}, $C_{8a''}$),

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152.6 (C_2, $C_{2''}$), 131.0 ($C_{2''''}$, $C_{3''''}$), 129.0 ($C_{2'}$, $C_{6'}$, $C_{2'''}$, $C_{6'''}$), 128.6 ($C_{3'}$, $C_{5'}$, $C_{3'''}$, $C_{5'''}$), 128.2 ($C_{4'}$, $C_{4'''}$,), 123.7 (C_5, $C_{5'}$), 122.4 (C_3, $C_{3''}$), 115.2 (C_{4a}, $C_{4a''}$), 114.6 (C_6, $C_{6'}$), 110.8 (C_8, $C_{8''}$), 55.7 ($2OCH_3$), 28.3 ($C_{1''''}$, $C_{4''''}$), 18.7 ($2CH_3$). HRMS (ESI) (*m/z*), $[M+H]^+$ calcd. For $C_{38}H_{32}O_6$: 585.2271, found : 585.2266.

(*E*)-8,8'-(But-2-ene-1,4-diyl)bis(2-ethyl-7-methoxy-3-phenyl-4*H*-chromen-4-one) (10b). Colourless solid; Yield: (52%); mp 227-229 ^oC; FT-IR (KBr, cm^{-1}) υ_{max}: 1635 (C=O). ^1H NMR (400 MHz, DMSO-d_6, δppm): 7.65 (d, 2H, *J* 8.4 Hz, H_5, $H_{5''}$), 7.42 (d, 4H, *J* 7.8 Hz, Ar-H), 7.41 (dd, 4H, *J* 7.8, 7.5 Hz, Ar-H), 7.33 (t, 2H, *J* 7.5 Hz, Ar-H), 7.10 (d, 2H, *J* 8.4 Hz, C_6, $C_{6''}$), 5.77 (t, 2H, *J* 6.4 Hz, $H_{2''''}$, $H_{3''''}$), 3.56 (s, 6H, $2OCH_3$), 3.27 (d, 4H, *J* 6.4 Hz, $H_{1''''}$, $H_{4''''}$), 2.62 (q, 4H, *J* 7.8 Hz, $2CH_2$), 1.23 (t, 6H, *J* 7.8 Hz, $2CH_3$). ^{13}C NMR (101 MHz, DMSO-d_6, δppm): 187.4 (C_4, $C_{4''}$), 158.7 (C_7, $C_{7''}$), 152.5 (C_{8a}, $C_{8a''}$, C_2, $C_{2''}$), 131.0 ($C_{2''''}$, $C_{3''''}$), 129.1 ($C_{2'}$, $C_{6'}$, $C_{2'''}$, $C_{6'''}$), 128.6 ($C_{3'}$, $C_{5'}$), 128.1 (C_5, $C_{5'}$), 128.0 ($C_{3'''}$, $C_{5'''}$), 123.7 ($C_{4'}$, $C_{4'''}$), 122.8 (C_3, $C_{3''}$), 114.6 (C_{4a}, $C_{4a''}$), 114.2 (C_6, $C_{6'}$), 110.8 (C_8, $C_{8''}$), 55.6 ($2OCH_3$), 28.3 ($C_{1''''}$, $C_{4''''}$), 24.5 ($2CH_2$).10.2 ($2CH_3$). HRMS (ESI) (*m/z*), $[M+H]^+$ calcd. For $C_{40}H_{36}O_6$: 613.2584, found: 613.257

Material and methods for cell culture

Anti-cell proliferation property of the newly synthesized compounds was assayed using MTT protocols. MTT [3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyl tetrazolium bromide], trypsin, EDTA Phosphate Buffered Saline (PBS) and were purchased from Sigma Chemicals Co. (St. Louis, MO) and Fetal Bovine Serum (FBS) were procured from Gibco. 25 cm^2 and 75 cm^2 flask and 96 well plate purchased from Eppendorf India. The cell lines were purchased from NCCS, Pune and the cells were maintained in RPMI–1640 mediums supplemented with 10% FBS and the antibiotics penicillin/streptomycin (0.5 mL^{-1}). MTT Assay is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl) -2,5-diphenyl tetrazolium bromide (MTT) by the enzymatic action of MSD. The MTT percolates in the cells and reaches the mitochondria get reduced into a purple coloured formazan precipitate which subsequently estimated calorimetrically at 570 nm to evaluate cellular viability. The experimental procedure was performed in triplicate with 6 variable µM concentrations. The % cellular anti-proliferation[34] by plotting dose-response curves with the help of origin software using following equation.

$$\% \text{ Inhibition} = \frac{100\ (\text{Control- Treatment})}{\text{Control}}$$

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Supplementary Material

Copies of ^1H NMR, ^{13}C NMR and HRMS spectra are given in the Supplementary Material file associated with this manuscript.

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