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Synthesis of Psoralidin derivatives and their anticancer activity: first synthesis of Lespeflorin I_1

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ABSTRACT

Synthetic scheme for the preparation of a number of different derivatives of anticancer natural product Psoralidin is described. A convergent synthetic approach is followed using simple starting materials like substituted phenyl acetic esters and benzoic acids. The developed synthetic route leads us to complete the first synthesis of an analogous natural product Lespeflorin I_1, a mild melanin synthesis inhibitor. Preliminary bioactivity studies of the synthesized compounds are carried out against two commonly used prostate cancer cell lines. Results show that the bioactivity of the compounds can be manipulated by the simple modification of the functional groups.

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1. Introduction

Psoralidin (**1**)[1] is a member of an emerging class of natural product called prenylated coumestanes which contain one or more isopentenyl group/s in the nucleus of 6*H*-benzofuro[3,2-*c*]chromen-6-one (Fig. 1). The natural product, in the crude mixture of its producer *Psoralea corylifolia* Linn, has been used as a traditional medicine in India and China from ancient time.[2] The compound itself also show a wide range of bioactive properties like antioxidant,[3] antidepressant,[4] antibacterial,[5] anti-diabetic,[6] antiviral,[7] anti-inflammatory,[8] and anti-osteoporosis.[9] It has also been found to be active against different types of cancer cells like gastric, breast, colon, bone, and stomach.[10] Research from different groups, including us, have shown that Psoralidin targets multiple signaling cascades and inhibits the proliferation of castration resistant prostate cancer cells by downregulation of MAPkinase signaling with little or almost zero toxicity.[10g,11a–d] In the same prostate cancer cells the compound also induces reactive oxygen species (ROS) mediated apoptosis.[11d] The IC_{50} values of Psoralidin (**1**) against two different prostate cancer cell lines, namely PC-3 and DU-145, are 60 μM and 45 μM, respectively. Our group is working on the anticancer properties of Psoralidin for a long time.[11a–d] But the relatively high IC_{50} value of the compound coupled with inherent low solubility brings a great deal of difficulty in further biological studies. It is to be mentioned that chemotherapeutic agents such as Docetaxel (IC_{50} ~ 5 nM),[11e,f] Cabazitaxel (IC_{50} ~ 10 nM)[11g] and Mitoxantrone (IC_{50} ~ 5 μM)[11h] have been reported to be active against prostate cancer cells (PC-3). Therefore, it is assumed that only a synthetic modification might help to improve the activity of the compound leading to further practical application.

There are a number of different methodologies reported in the literature for the synthesis of coumestanes.[12] But only a few of those processes are adopted for prenylated coumestanes,[12i–l] mainly because of the sensitivity of the compounds towards strong reagents and conditions. Thus the synthesis of analogs of Psoralidin is always a difficult task. Earlier, we have reported a convergent synthetic pathway for the total synthesis of Psoralidin.[12l] In this article, we have shown that a number of different derivatives of Psoralidin (**1**) can be prepared by the modification of our earlier reported[12l] pathway. In this context, we have also synthesized Lespeflorin I_1 (**2**), an 8-hydroxy analog of Psoralidin. The compound was isolated from the roots of *Lespedeza floribunda* Bunge and reported to act as a mild melanin synthesis inhibitor in normal human epidermal melanocytes.[13] The activities of all the synthesized compounds were tested against two different prostate cancer cell lines to get a preliminary idea about structure–activity relationship of the parent natural product.

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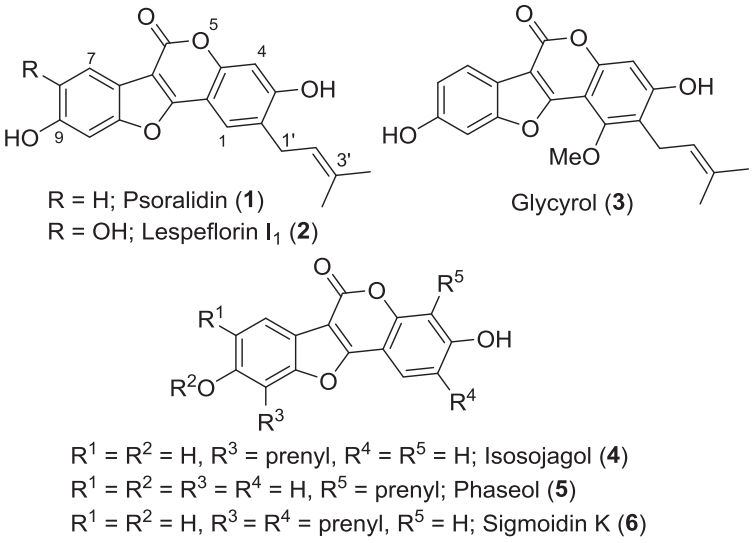
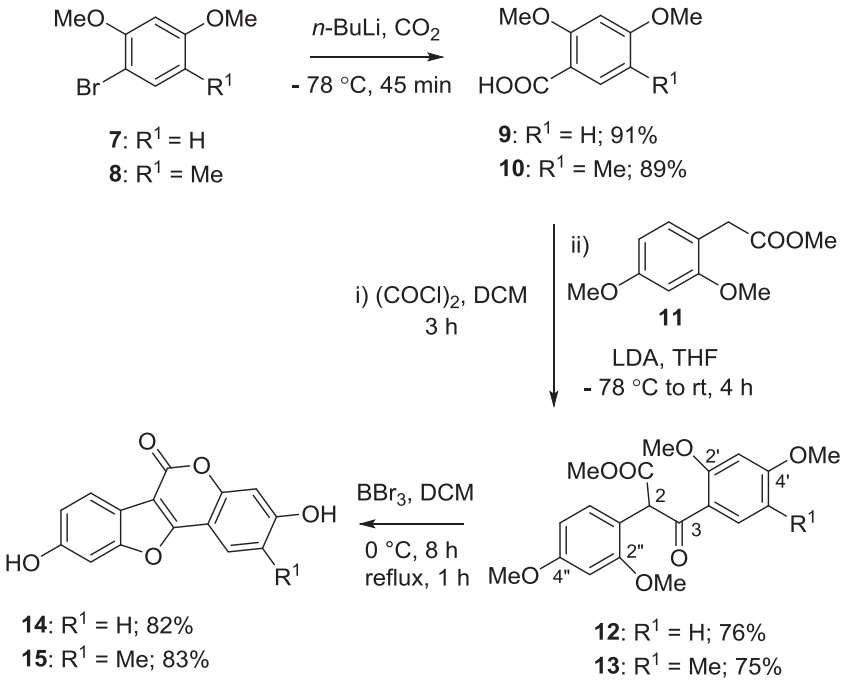


Fig. 1. Psoralidin and structurally similar bioactive natural products.

2. Results and discussion

We started with the attempt to synthesize derivatives like **14** & **15**, where the prenyl group of Psoralidin (**1**) was either absent or replaced with −Me (Scheme 1). The target was to evaluate the role of the existing prenyl group in the bioactivity pattern of the parent molecule. At this point it is to be mentioned that the prenyl group is the most sensitive functional group of the molecule which makes the synthesis process more difficult.[12l] The synthetic scheme started with 1-bromo-2,4-dimethoxybenzene (**7**) and 1-bromo-5-methyl-2,4-dimethoxybenzene (**8**) for the synthesis of **14** & **15**, respectively. Compound **8** was prepared from 1,5-dibromo-2,4-dimethoxy benzene by selective replacement of one of the bromine atom with methyl. Metalation of the bromine atom of **7** and **8** with *n*-butyl lithium followed by treatment with carbon dioxide produced acids **9** and **10**, respectively. Addition of the LDA generated anion of methyl 2-(2,4-dimethoxyphenyl)acetate (**11**) to acid chlorides of **9** and **10**, prepared by the treatment of oxalyl chloride, produced compounds **12** and **13**. It is to be noted that compound **11** was prepared by Perkin condensation of 2,4-dimethoxybenzaldehyde and hippuric acid following a reported procedure.[14] Finally, BBr_3 mediated one pot demethylation and cyclization sequence gave the desired Psoralidin derivatives **14** and **15**. Structural assignments of the new compounds were carried out using regular spectroscopic techniques including IR, ^1H, ^{13}C NMR and HRMS.

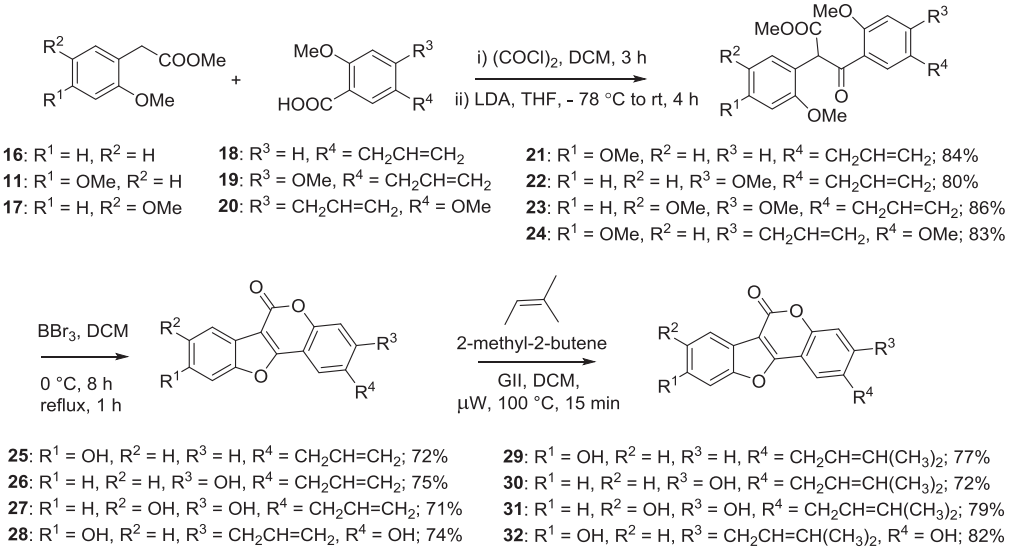
In the subsequent experiment, we decided to evaluate the function of the two hydroxyl groups and also the importance of their relative positions in the parent natural product. To this end we targeted four derivatives **29**–**32**, where compounds **29** and **30** had one of the hydroxyl groups missing from the C-3 and C-9 position of



Scheme 1. Synthesis of derivatives with substitution at C-2.

the parent Psoralidin, respectively. On the other hand, compound **31** and **32** carried all the same functional groups with altered position at C-8, C-9 and C-2, C-3, respectively. The starting materials for the synthesis were phenyl acetates **11**, **16**, **17** and benzoic acid derivatives **18**–**20** (Scheme 2). The acetates **16** and **17** were prepared from the corresponding hydroxyphenylacetic acids by methylation. Compound **18** was prepared from 4-allyl-2-bromo-1-methoxybenzene. Compound **19** and **20** were prepared in two steps from 1,5-dibromo-2,4-dimethoxybenzene and 1,4-dibromo-2,5-diemthoxybenzene, respectively, by sequential replacement of two bromine atoms with allyl and CO_2 (See Supplementary data). Acids **18**–**20** were converted to the corresponding acid chlorides and condensed with the LDA generated anions of phenyl acetates to produce compounds **21**–**24**. Next, the BBr_3-mediated demethylative cyclization yielded allylated coumestane derivatives **25**–**28**. Finally, a Grubb's metathesis reaction with 2-methylbut-2-ene provided the desired Psoralidin derivatives **29**–**32**. The structures of all the compounds were confirmed by ^1H and ^{13}C NMR spectroscopy, as well as HRMS.

Next, it was attempted to introduce extra hydroxyl groups in the parent nucleus of Psoralidin (**1**). To this end, we conceived the idea that hydroxyl groups might increase the activity as well as solubility of the molecule. So, we targeted to synthesize three derivatives **2**, **46**, and **47**, placing one excess hydroxyl group each in the C-8, C-4, and C-10 position of the natural product, respectively (Scheme 5). As discussed earlier, compound **2** is the natural product Lespeflorin I_1, which shows a mild melanin synthesis inhibitory property in normal human epidermal melanocytes.[13] Following a similar synthetic strategy as described earlier, we needed the phenylacetate derivatives **11**, **33**, **34** and benzoic acids **19**, **35** (Scheme 3). Synthesis of compound **33** was reported in the literature starting from 2,4,5-trimethoxybenzoic acid in six linear



16: R^1 = H, R^2 = H
11: R^1 = OMe, R^2 = H
17: R^1 = H, R^2 = OMe

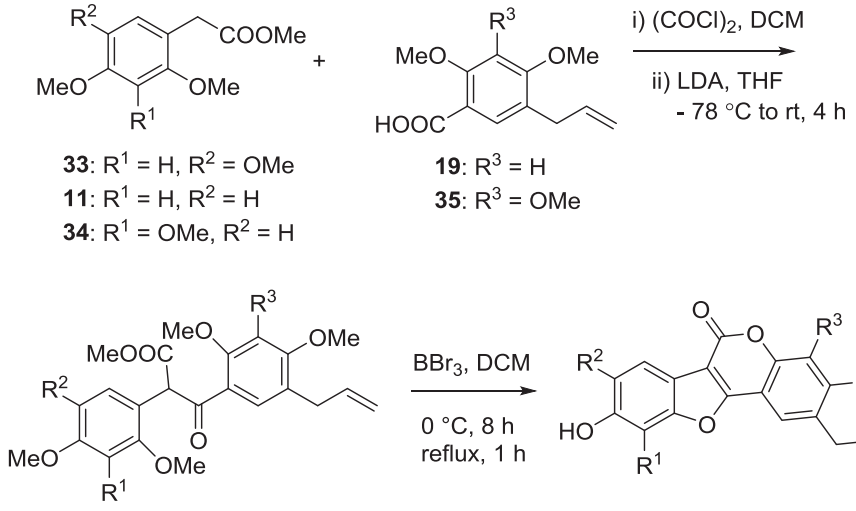
18: R^3 = H, R^4 = $CH_2CH{=}CH_2$
19: R^3 = OMe, R^4 = $CH_2CH{=}CH_2$
20: R^3 = $CH_2CH{=}CH_2$, R^4 = OMe

21: R^1 = OMe, R^2 = H, R^3 = H, R^4 = $CH_2CH{=}CH_2$; 84%
22: R^1 = H, R^2 = H, R^3 = OMe, R^4 = $CH_2CH{=}CH_2$; 80%
23: R^1 = H, R^2 = OMe, R^3 = OMe, R^4 = $CH_2CH{=}CH_2$; 86%
24: R^1 = OMe, R^2 = H, R^3 = $CH_2CH{=}CH_2$, R^4 = OMe; 83%

25: R^1 = OH, R^2 = H, R^3 = H, R^4 = $CH_2CH{=}CH_2$; 72%
26: R^1 = H, R^2 = H, R^3 = OH, R^4 = $CH_2CH{=}CH_2$; 75%
27: R^1 = H, R^2 = OH, R^3 = OH, R^4 = $CH_2CH{=}CH_2$; 71%
28: R^1 = OH, R^2 = H, R^3 = $CH_2CH{=}CH_2$, R^4 = OH; 74%

29: R^1 = OH, R^2 = H, R^3 = H, R^4 = $CH_2CH{=}CH(CH_3)_2$; 77%
30: R^1 = H, R^2 = H, R^3 = OH, R^4 = $CH_2CH{=}CH(CH_3)_2$; 72%
31: R^1 = H, R^2 = OH, R^3 = OH, R^4 = $CH_2CH{=}CH(CH_3)_2$; 79%
32: R^1 = OH, R^2 = H, R^3 = $CH_2CH{=}CH(CH_3)_2$, R^4 = OH; 82%

Scheme 2. Synthesis of Psoralidin analogs **29**–**32**.



33: R^1 = H, R^2 = OMe
11: R^1 = H, R^2 = H
34: R^1 = OMe, R^2 = H

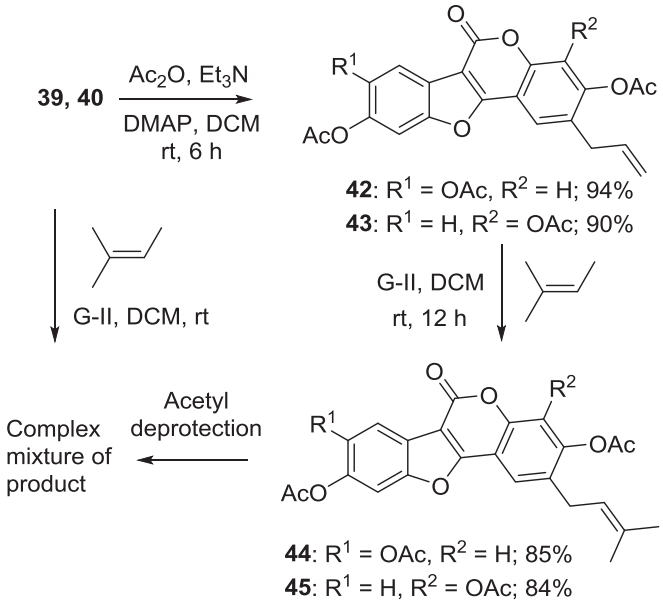
19: R^3 = H
35: R^3 = OMe

36: R^1 = H, R^2 = OMe, R^3 = H; 81%
37: R^1 = H, R^2 = H, R^3 = OMe; 76%
38: R^1 = OMe, R^2 = H, R^3 = H; 83%

39: R^1 = H, R^2 = OH, R^3 = H; 75%
40: R^1 = H, R^2 = H, R^3 = OH; 81%
41: R^1 = OH, R^2 = H, R^3 = H; 82%

Scheme 3. Synthesis of allylated coumestanes **39**–**41**.

steps.[15] To avoid the lengthy synthetic procedure and to follow a common synthetic route for all the similar compounds, we used an analogous procedure described for the synthesis of compound **11**.[14] We started with methoxy substituted benzaldehyde and used three convergent steps, i.e., a Perkin type condensation with hippuric acid, refluxing with $NaOH/H_2O_2$, and esterification, to produce all the three compounds **11**, **33**, and **34** in good overall yield (see Supplementary data). Compound **35** was prepared from 1,5-dibromo-2,3,4-trimethoxy benzene by sequential replacement of two bromine atoms with allyl and CO_2 (see Supplementary data). LDA mediated condensation of **33** & **11** with **19** & **35** produced compounds **36** & **37**, respectively. A similar reaction between **34** and **19** produced **38**. Next, BBr_3 mediated one pot demethylative cyclization produced allylated derivatives **39**–**41** (Scheme 3). The structures of compounds **36**–**41** were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, as well as HRMS.

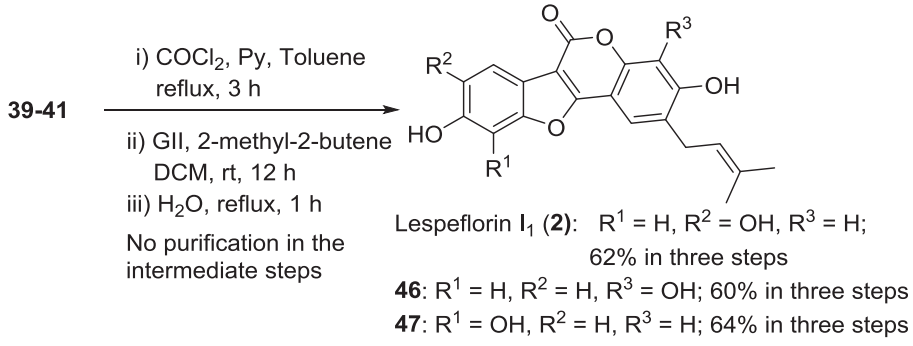


Scheme 4. Synthesis of triacetates and their deprotection.

Now, it was expected that a Grubb's catalyzed cross metathesis reaction with 2-methyl-2-butene would be sufficient to provide the targeted Psoralidin derivatives. But, the second generation Grubb's catalyzed cross metathesis reaction of both **39** and **40** with 2-methyl-2-butene ended up with producing a complex mixture of products (Scheme 4). In fact, it was observed that addition of the catalyst to the solution of **39** and **40** instantaneously destroyed the compounds at room temperature. In this context it should be mentioned that a similar reaction could easily be carried out during the total synthesis of Psoralidin.[12l] Possibly the presence of a catechol type motif in **39** and **40** made the compounds more vulnerable to oxidation. To stop the plausible transition metal catalyzed oxidation of the free catechol moiety, we decided to protect the hydroxyl groups with some easily removable functional groups. So, triacetates **42** and **43** were prepared from **39** and **40**, respectively, by the treatment with acetic anhydride in the presence of triethylamine. Now the cross metathesis reaction with 2-methyl-2-butene, catalyzed by second generation Grubb's catalyst at room temperature, produced **44** and **45** in very good yields. The experiment confirmed the role of the catechol moiety in the earlier reaction. But, we faced another hurdle during the deprotection of the acetyl group. All of the attempted acetyl deprotection strategies ended up with the formation of a complex mixture of products. Even very mild basic condition like $NaHCO_3/MeOH$[16] turned out to be harsh enough to destroy the compounds. We were unable to use any acidic reagents because of the reported sensitivity of the compounds towards very mild acidic condition.[12l] An attempted reaction at neutral environment using neutral alumina[17] in the conventional or microwave heating condition also failed to produce any isolable product.

To cope with this type of extremely sensitive compounds, we needed a very labile protecting group which could be opened up in neutral conditions without using any acidic or basic reagent. A possible use of benzyl as a protecting group, and hence a $H_2/Pd–C$ mediated reductive deprotection, was not considered because of the possibility of double bond reduction as well as palladium metal catalyzed oxidation. In this context, a cyclic carbonate protecting group was found to be a best fit to solve the problem. The cyclic carbonates can protect two *ortho*-hydroxy groups and open up easily by refluxing with water only. Thus, two *ortho*-hydroxyl groups of the compounds **39**–**41** were protected as a cyclic carbonate by refluxing with pyridine and phosgene in toluene.[18] An attempt to purify the products proved to be difficult because of the inherent instability of the cyclic carbonate protecting group which eventually opened up to give the starting materials back. So the product, after the removal of toluene and pyridine, was subjected to second generation Grubb's catalyzed cross metathesis reaction without any attempt of purification. Again in the next step, the crude product was subjected to a deprotection reaction by refluxing with water.[19] Final purification of the product, thus formed, yielded compound **2**, **46**, and **47**, as colorless solid (Scheme 5). As expected, all the physical and spectral characteristics of compound **2** were identical to the reported data of natural Lespeflorin I_1 (Table S1 in Supplementary data). Structures of other two compounds were also confirmed using IR, ^1H, ^{13}C NMR spectroscopy as well as HRMS.

Now, the activities of the synthesized compounds were compared with the parent natural product using two prostate cancer cell



Scheme 5. Synthesis of Lespeflorin I_1 (**2**) and analogs.

lines, namely PC-3 and DU-145. The prostate cancer cell lines were chosen because of the reported activity of Psoralidin against castration resistant prostate cancer cells.[10g,11a–d] For the experiment, the cells were treated with the dimethyl sulfoxide (DMSO) solution (final concentration of 0.002%) of the synthesized compounds and the cell viability was quantified using the trypan blue exclusion assay.[20] The natural product Psoralidin was used as a positive control and the vehicle (DMSO) as a negative control. Experiments on compound **14**–**15** and **25**–**28** showed that none of the compounds was able to carry out a reasonable inhibition of the growth of the cancer cells. The experiment established that the prenyl group was an essential functionality to preserve the bioactivity of the molecule. Similar was the result for compounds **29** and **30** which showed that the hydroxyl groups were also indispensable for the activity of the molecule. Compounds **31** and **32** showed very faint activity compared to the parent Psoralidin (**1**) (Table 1) confirming the relative positions of functional groups as equally important for the biological activity of the parent compound. Better results were obtained with the compounds having extra hydroxyl group. The natural product Lespeflorin I_1 (**2**) was almost equally active to Psoralidin (**1**) in PC3 cell line (IC_{50} ~ 68 μM). In case of DU145 cell line, the activity was even better (IC_{50} ~ 4 μM) (Table 1). Among the other two compounds, **47** was less active compared to Psoralidin (**1**). But, compound **46** showed very good activity against both the cell lines. With the IC_{50} value of ~14 μM and ~1 μM in PC3 and DU145 cell line, respectively, it was 5–45 times more active compared to the parent natural product **1**. Although, these results are not sufficient to explain the exact reason of the enhancement of the activity of compound **46**, it may be assumed that the hydroxyl group in the C-4 position increases the hydrogen bonding with the target protein. On the other hand, the –OH group in the C-10 position of **47** most probably increases the steric hindrance and inhibits the desired interaction between protein and C9-OH. As expected, due to the acetyl protection of the free hydroxyl groups, compounds **44** and **45** were completely inactive.

Table 1
Comparison of anti-proliferative activity of Psoralidin and synthetic derivatives in two different prostate cancer cell lines

Compound	Cytotoxicity PC3 cells (IC_{50}, μM)[a]	Cytotoxicity DU145 cells (IC_{50}, μM)[a]
Psoralidin (**1**)	60±3	45±5
Lespeflorin I_1 (**2**)	68±5	4±1
31	125±10	110±10
32	95±8	58±5
46	14±2	1±0.5
47	120±10	76±8

[a] Measured in triplicate using trypan blue exclusion assay method.

3. Conclusion

In conclusion, we synthesized a few different derivatives of Psoralidin by the elimination of an existing functional group or addition of a new functional group in the original skeleton of the natural product. The activities of the synthetic compounds were tested against two different prostate cancer cell lines. Structure–activity relationship (SAR) studies revealed that introduction of a hydroxyl group in the appropriate position of the molecule increased the activity in many fold. We have also reported the first synthesis of Lespeflorin I_1 (**2**). The compound was found to be active against prostate cancer cell lines in addition to its earlier known melanin synthesis inhibitory property. The success of this work encourages future exploration of related structures to obtain even more active compounds.

4. Experimental

4.1. General remarks

Reactions in anhydrous condition were conducted in flame-dried glass apparatus under N_2 atmosphere. THF was freshly distilled from sodium and benzophenone and DMF, CH_2Cl_2 and *i*-Pr_2NH was distilled from CaH_2. Chromatographic separations were performed using silica gel 60–120 and 230–400. All commercially available reagents were used as received. Melting points are uncorrected. Infrared (IR) spectra were recorded using an FT-IR spectrometer, either as a pressed thin KBr disks or as chloroform solutions on sodium chloride disks. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at 500 (^1H)/125 (^{13}C) MHz in the indicated solvents. High resolution (HRMS) mass spectra were obtained using electron impact (EI) ionization techniques on a magnetic sector instrument at a resolution greater than 10,000. Microwave reactions were carried out either on a Biotage Initiator 2.0 instrument or Discover labmate focused™ microwave applicator (standard configuration, temperature control, external IR temperature sensor, fixed hold time). HPLC purification was carried out using a Symmetry Prep C_{18}, 7 μm column (19×150 mm) on a binary LC system.

4.1.1. Cell culture. Human prostate cancer cell lines PC-3 and DU-145 were grown in Dulbecco's modified Eagle's medium and RPMI-1640, respectively, and supplemented with 10% fetal bovine serum with antibiotics. Psoralidin and derivatives were dissolved in dimethyl sulfoxide (DMSO) and the cells were treated with DMSO at a final concentration of 0.002%. Cell viability was quantified using the trypan blue exclusion assay. After 24 h treatment with Psoralidin and Psoralidin derivatives, cells were washed with PBS. A collection of supernatants and adherent cells obtained by trypsinization were incubated in 0.4% trypan blue (Corning, Manassas, VA) at 1:1 ratio and pipetted onto a hemacytometer and manually counted under a microscope at ×20 magnification. **20** Psoralidin was used as a positive control and vehicle (DMSO) as a negative control.

*4.1.2. Lespeflorin I_1 (**2**).*[13] This compound was prepared from **39** in three steps without purification of any intermediates. To a stirred solution of **39** (14 mg, 0.04 mmol) in toluene (20 mL), pyridine (0.3 mL) and phosgene (0.3 mL) was added. The mixture was refluxed under nitrogen atmosphere for 3 h and then allowed to cool. 10% HCl (5 mL) was added under ice cold condition and the mixture was extracted with ether (30 mL) immediately. The organic layer was washed with water (2×10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated under vacuum. Remaining toluene was removed by repeated co-evaporation with ethyl acetate. The brown solid compound, thus produced, was dissolved in CH_2Cl_2 (20 mL) and degassed. To this mixture degassed 2-methyl-2-butene (2 mL) and Grubb's second generation catalyst (3 mg, 0.0035 mmol) was added and allowed to stir at room temperature for 12 h under nitrogen atmosphere. After completion of the reaction, as checked by TLC, it was concentrated under vacuum and extracted with ethyl acetate (2×20 mL). The organic layer was washed with water (2×10 mL) and concentrated to get a light brown solid which was dissolved in THF (5 mL) and water (5 mL). The mixture was refluxed for 1 h and then THF was removed. Extraction with ethyl acetate (2×20 mL) and subsequent washing with water (2×10 mL), brine (10 mL), drying (Na_2SO_4) and concentration produced crude compound **2**. It was finally purified by reverse phase semi preparative HPLC (symmetry C_{18}, 7 μm, solvent gradient 9:1 CH_3CN:H_2O) to get the natural product Lespeflorin I_1 (**2**) (9.5 mg, 62% over three steps) as a brownish solid. R_f 0.5 (1:3:9 methanol:ethyl acetate:hexane); mp>360 °C, chars at 210 °C; ν_{max} (film) cm^{-1} 1718, 1629, 1490, 1267, 1161, 1002; ^1H NMR (DMSO-d_6, 500 MHz) δ) δ 10.73 (br s, 1H, OH), 9.55 (br s, 1H, OH), 9.42 (br s, 1H, OH), 7.60 (s, 1H, C1-H), 7.23 (s, 1H,

C7-H), 7.18 (s, 1H, C10-H), 6.91 (s, 1H, C4-H), 5.35 (t, 1H, *J*=8.0 Hz, C2′-H), 3.32 (d, 2H, *J*=8.0 Hz, C1′-H_2), 1.74 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.2 (C), 158.7 (C), 158.0 (C), 152.7 (C)148.9 (C), 145.6 (C), 144.4 (C), 132.6 (C), 126.4 (C), 121.8 (CH), 120.8 (CH), 114.2 (C), 104.9 (CH), 104.1 (C), 102.4 (CH), 102.2 (C), 99.0 (CH), 27.6 (CH_2), 25.7 (CH_3), 17.7 (CH_3); HRMS (EI+) *m/z* 352.0950 ([M]$^+$ $C_{20}H_{16}O_6$, requires 352.0946).

*4.1.3. 1-Bromo-2,4-dimethoxy-5-methylbenzene (**8**).* 4,6-Dimethoxy-1,3-dibromobenzene[21] (1.50 g, 5.07 mmol) was added to a solution of *i*-PrMgCl (1 M in THF, 7 mL, 7 mmol) at −10 °C under N_2 atmosphere. After 45 min, methyl iodide (0.5 mL, 7.7 mmol) was added drop wise, and the mixture was allowed to stir at the same temperature for 30 min and then at rt for 4 h. The reaction was quenched by the addition of 10% HCl (15 mL). THF was removed in vacuum, and the mixture was extracted with ethyl acetate (2×50 mL). The organic layer was washed with water (2×30 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The resulting crude compound was purified by column chromatography to get **8** (950 mg, 81%) as a colorless liquid. R_f 0.6 (1:10 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1555, 1222, 1143, 1045; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (s, 1H, C6-H), 6.42 (s, 1H, C3-H), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.1 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$,125 MHz): δ 157.8 (C), 154.6 (C), 133.8 (CH), 120.0 (C), 100.8 (C), 96.2 (CH), 56.3 (CH_3), 55.5 (CH_3), 15.1 (CH_3); HRMS (EI+) *m/z* 229.9946 ([M]$^+$ $C_9H_{11}BrO_2$, requires 229.9942).

*4.1.4. 2,4-Dimethoxybenzoic acid (**9**).*[22] *n*-BuLi (2.5 M in THF, 3.3 mL, 8.3 mmol) was added drop wise to a stirred solution of 1-bromo-2,4-dimethoxybenzene (**7**) (1.5 g, 6.9 mmol) in THF (15 mL) at −78 °C under N_2 atmosphere. After 30 min, CO_2 gas was passed through the solution during 45 min of time and the mixture was allowed to warm up to room temperature. THF was removed in vacuum and the mixture was treated with saturated $NaHCO_3$ solution (40 mL). The water layer was washed with ethyl acetate (2×20 mL) and then acidified with conc. HCl. The mixture was extracted with ethyl acetate (2×75 mL). The organic layer was washed with water (2×30 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated. Recrystallization from ethyl acetate produced **9** (1.15 g, 91%) as white solid. R_f 0.3 (1:1 ethyl acetate:hexane); mp 103–105 °C (lit.[22] 107–109 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, 1H, *J*=9.0 Hz, C6-H), 6.61 (dd, 1H, *J*=9.0, 2.0 Hz, C5-H), 6.50 (d, 1H, *J*=2.0 Hz, C3-H), 4.01 (s, 3H, OMe), 3.86 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.9 (C), 165.2 (C), 160.2 (C), 135.2 (CH), 110.1 (C), 106.2 (CH), 98.5 (CH), 56.4 (CH_3), 55.7 (CH_3).

*4.1.5. Methyl 2,3-bis(2,4-dimethoxyphenyl)-3-oxopropanoate (**12**).*[12c] To a stirred solution of acid **9** (320 mg, 1.76 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere, DMF (one drop) and oxalyl chloride (0.23 mL, 2.6 mmol) were added. The mixture was stirred for 3 h at room temperature and then the solvent was removed under vacuum. The crude product acid chloride was directly used for the next reaction without further purification. A solution of compound **11**[14] (554 mg, 2.64 mmol) in THF (6 mL) was added at −78 °C to a freshly prepared solution of LDA, prepared from *n*-BuLi (2.5 M in THF, 1.44 mL, 3.52 mmol) and *i*-Pr_2NH (0.49 mL, 3.52 mmol) in THF (5 mL) at 0 °C under N_2 atmosphere. The thus produced yellowish anion was stirred at −78 °C for 45 min and then a solution of crude acid chloride in THF (10 mL) was added drop wise. The reaction was stirred at the same temperature for another 45 min and then at room temperature for 4 h. 10% HCl (10 mL) was added to quench the reaction, THF was removed in vacuum and the water layer was extracted with ethyl acetate (2×50 mL). The organic layer was washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography to get **12** (500 mg, 76%) as yellowish oily compound. R_f 0.3 (1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, 1H, *J*=9.0 Hz, C6′-H), 7.03 (d, 1H, *J*=8.5 Hz, C6″-H), 6.49 (dd, 1H, *J*=9.0, 2.0 Hz, C5′-H), 6.44 (s, 1H, C3′-H), 6.41 (d, 1H, *J*=8.5 Hz, C5″-H), 6.36 (d, 1H, *J*=2.0 Hz, C3″-H), 5.95 (s, 1H, C2-H), 3.78 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.72 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.1 (C), 171.0 (C), 164.9(C), 160.7 (C), 160.3(C), 157.9 (C), 133.5 (CH), 130.3 (CH), 119.5 (C), 115.6 (C), 105.7 (CH), 104.2 (CH), 98.5 (CH), 98.0 (CH), 57.2 (CH_3), 55.5 (CH_3), 55.5 (CH_3), 55.2 (CH_3), 55.2 (CH_3), 52.2 (CH); HRMS (EI+) *m/z* 374.1370 ([M]$^+$ $C_{20}H_{22}O_7$, requires 374.1366).

*4.1.6. Methyl 3-(2,4-dimethoxy-5-methylphenyl)-2-(2,4-dimethoxyphenyl)-3-oxopropanoate (**13**).* This compound was prepared from compound **8** in three steps without purifying the intermediate acid and acid chloride. *n*-BuLi (2.5 M in THF, 0.87 mL, 2.18 mmol) was added drop wise to a stirred solution of **8** (420 mg, 1.82 mmol) in THF (10 mL) at −78 °C under N_2 atmosphere. After 30 min CO_2 gas was passed through the solution during 45 min of time and the mixture was allowed to warm up to room temperature. THF was removed in vacuum and the mixture was treated with saturated $NaHCO_3$ solution (30 mL). The water layer was washed with ethyl acetate (2×15 mL) and then acidified with conc. HCl. The mixture was extracted with ethyl acetate (2×50 mL). The organic layer was washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated to get the acid **10** (320 mg). Without further purification it was dissolved in CH_2Cl_2 (10 mL) under N_2 atmosphere, DMF (one drop) and oxalyl chloride (0.23 mL, 2.6 mmol) were added. The mixture was stirred for 3 h at room temperature and then the solvent was removed in vacuum to yield the corresponding acid chloride, which was again directly used for the next reaction without further purification. A solution of compound **11**[14] (514 mg, 2.45 mmol) in THF (7 mL) was added at −78 °C to a freshly prepared solution of LDA, prepared from *n*-BuLi (2.5 M in THF, 1.3 mL, 3.26 mmol) and *i*-Pr_2NH (0.45 mL, 3.26 mmol) in THF (5 mL) at 0 °C under N_2 atmosphere. The thus produced yellowish anion was stirred at −78 °C for 45 min and then a solution of crude acid chloride, prepared earlier, in THF (10 mL) was added drop wise. The reaction was stirred at the same temperature for another 45 min and then at room temperature for 4 h. 10% HCl (10 mL) was added to quench the reaction, THF was removed in vacuum and the water layer was extracted with ethyl acetate (2×50 mL). The organic layer was washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography to get **13** (480 mg, 68% in three steps) as yellowish oily compound. R_f 0.5 (1:1 ethyl acetate:hexane); ν_{max} ($CHCl_3$) cm^{-1} 1732, 1659, 1608, 1508, 1463, 1211, 1029; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 (s, 1H, C6′-H), 7.01 (d, 1H, *J*=8.5 Hz, C6″-H), 6.43 (s, 1H, C3′-H), 6.41 (d, 1H, *J*=8.5 Hz, C5″-H), 6.28 (s, 1H, C3″-H), 5.94 (s, 1H, C2-H), 3.82 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, CO_2CH_3), 2.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.1 (C), 171.1 (C), 163.0 (C), 160.3 (C), 159.6 (C), 157.9 (C), 133.1 (CH), 130.1 (CH), 118.9 (C), 118.0 (C), 115.8 (C), 104.1 (CH), 98.4 (CH), 94.1 (CH), 57.2 (CH_3), 55.5 (CH_3), 55.3 (CH_3), 55.2 (CH_3), 55.2 (CH_3), 52.1 (CH), 15.3 (CH_3); HRMS (EI+) *m/z* 388.1529 ([M]$^+$ $C_{21}H_{24}O_7$, requires 388.1521).

*4.1.7. 3,9-Dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**14**).*[12c] BBr_3 (1 M in CH_2Cl_2, 6.1 mL, 6.1 mmol) was added at 0 °C to a solution of **12** (450 mg, 1.23 mmol) in CH_2Cl_2 (15 mL) under N_2 atmosphere. The mixture was stirred at same temperature for 10 h and quenched by the addition of water (10 mL). CH_2Cl_2 was removed in vacuum and the mixture was heated to reflux for 1 h. The water layer was extracted with ethyl acetate (2×40 mL). The organic layer was washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography to get compound **14** (270 mg, 82%) as brown solid. R_f 0.3 (1:1 ethyl acetate:hexane); mp>360 °C (lit.[12c] 350–360 °C); ^{1}H NMR

(DMSO-d_6, 500 MHz): δ 7.80 (d, 1H, J=8.5 Hz, C7-H), 7.66 (d, 1H, J=8.5 Hz, C1-H), 7.13 (d, 1H, J=2.0 Hz, C10-H), 6.92 (dd, 1H, J=8.5, 2.0 Hz, C8-H), 6.89 (dd, 1H, J=8.5, 2.0 Hz, C2-H), 6.88 (d, 1H, J=2.0 Hz, C4-H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.2 (C), 159.5 (C), 157.6 (C), 157.0 (C), 156.0 (C), 154.7 (C), 122.7 (CH), 120.7 (CH), 114.6 (C), 114.0 (CH), 113.8 (CH), 104.2 (C), 103.1 (CH), 102.1 (C), 98.7 (CH); HRMS (EI+) m/z 268.0376 ([M]$^+$ $C_{15}H_8O_5$, requires 268.0372).

*4.1.8. 3,9-Dihydroxy-2-methyl-6H-benzofuro[3,2-c]chromen-6-one (**15**).* This compound was prepared by the BBr_3 mediated demethylative cyclization of **13** following the identical procedure as described for the transformation of **12** to **14**. Yield 83%; R_f 0.4 (1:1 ethyl acetate:hexane); mp>360 °C; ν_{max} (film) cm^{-1} 1720, 1631, 1600, 1424, 1237, 1093; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.69 (s, 1H, C1-H), 7.66 (d, 1H, J=8.0 Hz, C7-H), 7.13 (d, 1H, J=2.0 Hz, C10-H), 6.92 (dd, 1H, J=8.0, 2.0 Hz, C8-H), 6.89 (s, 1H, C4-H), 2.21 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 159.5 (C), 159.4 (C), 157.8 (C), 157.0 (C), 155.9 (C), 152.9 (C), 123.0(C), 122.4 (CH), 120.6 (CH), 114.7 (C), 113.9 (CH), 103.7 (C), 102.1 (CH), 101.9 (C), 98.7 (CH), 15.6 (CH_3); HRMS (EI+) m/z 282.0523 ([M]$^+$ $C_{16}H_{10}O_5$, requires 282.0528).

*4.1.9. Methyl 2-(2-methoxyphenyl)acetate (**16**).*[23] To a stirred solution of 2-hydroxyphenylacetic acid (1.04 g, 6.8 mmol) in acetone (30 mL), K_2CO_3 (2.83 g, 20.5 mmol) and MeI (1.06 mL, 17.1 mmol) was added. The mixture was stirred at room temperature for 12 h and then acetone was removed at vacuum. Water (20 mL) was added to the mixture and extracted with ethyl acetate (2×30 mL). The organic layer was washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography to get **16** (1.10 g, 89%) as colorless oil. R_f 0.5 (1:20 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, 1H, J=8.0 Hz, C6′-H), 7.16 (d, 1H, J=8.0 Hz, C3′-H), 6.92–6.85 (m, 2H, C4′-H & C5′-H), 3.80 (s, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.62 (s, 2H, C2-H_2).

*4.1.10. Methyl 2,5-dimethoxyphenylacetate(**17**).*[24] To a stirred solution of 2,5-dimethoxyphenylacetic acid (**17a**, 1.01 g, 5.1 mmol) in dry methanol (10 mL), $SOCl_2$ (0.56 mL, 7.65 mmol) was added at 0 °C. The reaction was stirred at room temperature for 4 h and then methanol was removed at vacuum. Residue was dissolved in ethyl acetate (50 mL) and washed with water (2×20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated. Chromatographic purification produced **17** (980 mg, 91%) as colorless oil. R_f 0.4 (1:10 ethyl acetate:hexane); mp 62–64 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.80–6.74 (m, 3H, C3′-H, C4′-H & C6′-H), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.59 (s, 2H, C2-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7 (C), 153.2 (C), 151.5 (C), 123.8 (C), 116.8 (CH), 112.4 (CH), 111.2 (CH), 55.6 (CH_3), 55.2 (CH_3), 51.4 (CH_3), 35.4 (CH_2); HRMS (EI+) m/z 210.0896 ([M]$^+$ $C_{11}H_{14}O_4$, requires 210.0892).

*4.1.11. 5-Allyl-2-methoxybenzoic acid (**18**).* This semi solid compound was prepared from 4-allyl-2-bromo-1-methoxybenzene, following a similar procedure as described for the transformation of **7** to **9**. Yield 97%; R_f 0.4 (1:1 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1639, 1498, 1428, 1246, 1178, 1016; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, 1H, J=2.5 Hz, C6-H), 7.34 (dd, 1H, J=8.0, 2.5 Hz, C4-H), 6.95 (d, 1H, J=8.0 Hz, C3-H), 5.98–5.80 (m, 1H, C2′-H), 5.10–4.98 (m, 2H, C3′-H_2), 4.00 (s, 3H, OCH_3), 3.31 (d, 2H, J=7.0 Hz, C1′-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4 (C), 156.6 (C), 136.4 (CH), 134.9 (CH), 133.0 (C), 132.6 (CH), 117.0 (CH_2), 115.9 (C), 111.7 (CH), 56.3 (CH_3), 38.5 (CH_2); HRMS (EI+) m/z 192.0784 ([M]$^+$ $C_{11}H_{12}O_3$, requires 192.0786).

*4.1.12. 4-Allyl-2,5-dimethoxybenzoic acid (**20**).* This compound was obtained as white solid from 1-allyl-4-bromo-2,5-dimethoxybenzene (see Supplementary data) following an analogous reaction sequence as described for the transformation of **7** to **9**. Yield 94%; R_f 0.3 (1:1 ethyl acetate:hexane); mp 103–105 °C; ν_{max} (film) cm^{-1} 1682, 1509, 1430, 1273, 1219, 1039; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (s, 1H, C6-H), 6.81 (s, 1H, C3-H), 5.98–5.82 (m, 1H, C2′-H), 5.10–5.00 (m, 2H, C3′-H_2), 3.97 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.35 (d, 2H, J=7.0 Hz, C1′-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7 (C), 152.2 (C), 151.7 (C), 136.6 (CH), 135.1 (CH), 116.6 (CH_2), 115.3 (C), 113.5 (C), 113.4 (CH), 57.0 (CH_3), 55.8 (CH_3), 34.3 (CH_2); HRMS (EI+) m/z 222.0899 ([M]$^+$ $C_{12}H_{14}O_4$, requires 222.0892).

*4.1.13. Methyl 3-(5-allyl-2-methoxyphenyl)-2-(2,4-dimethoxyphenyl)-3-oxopropanoate (**21**).* This compound was obtained as yellowish oil from compound **18** and **11** following an identical method as described for the preparation of **12**. Yield 84%; R_f 0.4 (1:3 ethyl acetate:hexane); ν_{max} ($CDCl_3$) cm^{-1} 1737, 1679, 1610, 1508, 1463, 1159, 1032; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, 1H, J=2.5 Hz, C6′-H), 7.24 (dd, 1H, J=8.5, 2.5 Hz, C4′-H), 7.05 (d, 1H, J=8.0 Hz, C6″-H), 6.81 (d, 1H, J=8.5 Hz, C3′-H), 6.42 (dd, 1H, J=8.0, 2.5 Hz, C5″-H), 6.41 (d, 1H, J=2.5 Hz, C3″-H), 5.94 (s, 1H, C2-H), 5.94–5.84 (m, 1H, C2‴-H), 5.08–4.95 (m, 2H, C3‴-H_2), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.30 (d, 2H, J=6.5 Hz, C1‴-H_2). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.0 (C), 170.6 (C), 160.5 (C), 157.9 (C), 157.2 (C), 137.1 (CH), 134.3 (CH), 132.2 (C), 131.2 (CH), 130.4 (CH), 126.4 (C), 116.0 (C), 115.3 (CH_2), 111.7 (CH), 104.2 (CH), 98.5 (CH), 57.4 (CH_3), 55.5 (CH_3), 55.3 (CH_3), 55.2 (CH_3), 52.2 (CH), 39.0 (CH_2); HRMS (EI+) m/z 384.1568 ([M]$^+$ $C_{22}H_{24}O_6$, requires 384.1572).

*4.1.14. Methyl 3-(5-allyl-2,4-dimethoxyphenyl)-2-(2-methoxyphenyl)-3-oxopropanoate (**22**).* This compound was obtained as yellowish oil from compound **16** and **19** following an analogous reaction sequence as described for the preparation of **12**. Yield 80%; R_f 0.5 (1:3 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1737, 1658, 1604, 1463, 1272, 1129, 1027; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (s, 1H, C6′-H), 7.26–7.21 (m, 1H, C6″-H), 7.15–7.11 (m, 1H, C5″-H), 6.95–6.90 (m, 2H, C4″-H & C3″-H), 6.31 (s, 1H, C3′-H), 6.02 (s, 1H, C2-H), 5.98–5.80 (m, 1H, C2‴-H), 5.05–4.90 (m, 2H, C1‴-H_2), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.27 (d, 2H, J=6.5 Hz, C1‴-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.7 (C), 170.9 (C), 162.6 (C), 159.9 (C), 156.9 (C), 136.5 (CH), 132.8 (CH), 129.7 (CH), 128.8 (CH), 123.4 (C), 121.2 (C), 120.5 (CH), 118.3 (C), 115.6 (CH2), 110.4 (CH), 94.3 (CH), 57.9 (CH_3), 55.6 (CH_3), 55.3 (CH_3), 52.2 (CH_3), 33.4 (CH_2); HRMS (EI+) m/z 384.1570 ([M]$^+$ $C_{22}H_{24}O_6$, requires 384.1573).

*4.1.15. Methyl 3-(5-allyl-2,4-dimethoxyphenyl)-2-(2,5-dimethoxyphenyl)-3-oxopropanoate (**23**).* This compound was obtained as yellowish oil from compound **17** and **19** following an identical reaction sequence as described for the preparation of **12**. Yield 86%; R_f 0.5 (1:3 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1730, 1685, 1630, 1450, 1220, 1070; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (s, 1H, C6′-H), 6.77 (s, 1H, C6″-H), 6.81–6.69 (m, 2H, C3″-H & C4″-H), 6.31 (s, 1H, C3′-H), 5.97 (s, 1H, C2-H), 5.95–5.85 (m, 1H, C2‴-H), 5.05–4.95 (m, 2H, C3‴-H_2), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 3.25 (d, 2H, J=6.5 Hz, C1‴-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.5 (C), 170.6 (C), 162.6 (C), 159.9 (C), 153.3 (C), 151.2 (C), 136.4 (CH), 132.7 (CH), 124.4 (C), 121.2 (C), 118.3 (CH), 116.0 (CH_2), 115.6 (CH), 113.2 (CH), 111.4 (C), 94.4 (CH), 57.9 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 55.5 (CH_3), 55.2 (CH_3), 52.2 (CH), 33.4 (CH_2); HRMS (EI+) m/z 414.1674 ([M]$^+$ $C_{23}H_{26}O_7$, requires 414.1678).

*4.1.16. Methyl 3-(4-allyl-2,5-dimethoxyphenyl)-2-(2,4-dimethoxyphenyl)-3-oxopropanoate (**24**).* This compound was obtained as yellowish oil from compound **20** and **11** following the similar procedure as described for the preparation of **12**. Yield 83%; R_f 0.5 (1:3 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1736, 1672, 1611, 1508, 1400, 1210, 1039; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (s, 1H, C6′-

H), 7.02 (d, 1H, *J*=9.0 Hz, C6″-H), 6.71 (s, 1H, C3′-H), 6.41 (s, 1H, C3″-H), 6.38 (d, 1H, *J*=9.0 Hz, C5″-H), 5.99 (s, 1H, C2-H), 5.96–5.82 (m, 1H, C2‴-H), 5.08–4.98 (m, 2H, C3‴-H_2), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.64 (s, 3H, CO_2CH_3), 3.32 (d, 2H, *J*=6.5 Hz, C1‴-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.3 (C), 170.3 (C), 160.0 (C), 157.5 (C), 153.0 (C), 150.8 (C), 135.6 (CH), 135.3 (CH), 129.7 (CH), 123.7 (C), 115.9 (CH_2), 115.1 (C), 113.3 (C), 111.5 (CH), 103.8 (CH), 98.0 (CH), 56.9 (CH_3), 55.3 (CH_3), 55.1 (CH_3), 54.9 (CH_3), 54.7 (CH_3), 51.6 (CH), 34.0 (CH_2); HRMS (EI+) *m*/*z* 414.1677 ($[M]^+$ $C_{23}H_{26}O_7$, requires 414.1679).

*4.1.17. 2-Allyl-9-hydroxy-6H-benzofuro[3,2-c]chromen-6-one (**25**).* This compound was prepared by the BBr_3 mediated demethylative cyclization of **21** as described for the synthesis of **14**. Yield 72%; R_f 0.3 (1:1 ethyl acetate:hexane); mp 217–219 °C; ν_{max} (film) cm^{-1} 1707, 1625, 1508, 1250, 1076; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.29 (br s, 1H, OH), 7.65 (d, 1H, *J*=8.0 Hz, C7-H), 7.61 (s, 1H, C1-H), 7.39–7.34 (m, 2H, C4-H & C3-H), 7.11 (d, 1H, *J*=2.0 Hz, C10-H), 6.92 (dd, 1H, *J*=8.0, 2.0 Hz, C8-H), 6.00–5.92 (m, 1H, C2′-H), 5.18–5.05 (m, 2H, C3′-H_2), 3.41 (d, 2H, *J*=7.0 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.5 (C), 157.9 (C), 157.7 (C), 156.6 (C), 151.3 (C), 137.2 (CH), 137.1 (C), 132.3 (CH), 121.4 (CH), 120.5 (CH), 117.3 (CH), 117.0 (CH_2), 114.7 (C), 114.6 (C), 112.1 (CH), 105.5 (C), 98.9 (CH), 26.1 (CH_2); HRMS (EI+) *m*/*z* 292.0733 ($[M]^+$ $C_{18}H_{12}O_4$, requires 292.0736).

*4.1.18. 2-Allyl-3-hydroxy-6H-benzofuro[3,2-c]chromen-6-one (**26**).* The BBr_3 mediated demethylative cyclization of **22** to synthesize this compound was similar to that described for the synthesis of **14**. Yield 75%; R_f 0.3 (1:1 ethyl acetate:hexane); mp 262–264 °C; ν_{max} (film) cm^{-1} 1697, 1625, 1597, 1419, 1257, 1141, 1012; ^{1}H NMR (Acetone-d_6, 500 MHz) δ 8.01–7.96 (m, 1H, C7-H), 7.75 (s, 1H, C1-H), 7.74–7.72 (m, 1H, C10-H), 7.50–7.46 (m, 2H, C8-H & C9-H), 7.00 (s, 1H, C4-H), 6.12–6.06 (m, 1H, C2′-H), 5.25–5.10 (m, 2H, C3′-H_2), 3.52 (d, 2H, *J*=7.0 Hz, C1′-H_2); ^{13}C NMR (Acetone-d_6, 125 MHz) δ 160.9 (C), 159.3 (C), 157.5 (C), 155.1 (C), 154.3 (C), 136.2 (CH), 125.1 (CH), 124.0 (C), 123.8 (C), 123.0 (C), 122.4 (CH), 120.7 (C), 115.8 (CH), 111.7 (CH_2), 104.5 (C), 102.8 (CH), 33.1 (CH_2); HRMS (EI+) *m*/*z* 292.0733 ($[M]^+$ $C_{18}H_{12}O_4$, requires 292.0735).

*4.1.19. 2-Allyl-3,8-dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**27**).* This white solid compound was prepared by the BBr_3 mediated demethylative cyclization of **23** following a similar protocol for the synthesis of **14**. Yield 71%; R_f 0.3 (1:4:12 methanol:ethyl acetate:hexane); mp 322–324 °C; ν_{max} (film) cm^{-1} 1724, 1636, 1599, 1420, 1272, 1163, 1009; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.74 (br s, 1H, OH), 9.60 (br s, 1H, OH), 7.49 (d, 1H, *J*=9.0 Hz, C10-H), 7.46 (s, 1H, C1-H), 7.19 (d, 1H, *J*=3.0 Hz, C7-H), 6.83 (dd, 1H, *J*=9.0, 3.0 Hz, C9-H), 6.81 (s, 1H, C4-H), 6.05–5.95 (m, 1H, C2′-H), 5.20–5.05 (m, 2H, C3′-H_2), 3.30 (d, 2H, *J*=6.5 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8 (C), 159.3 (C), 157.5 (C), 155.1 (C), 153.4 (C), 148.4 (C), 136.1 (CH), 125.0 (C), 124.0 (CH), 121.6 (CH), 116.5 (CH_2), 114.1 (C), 112.2 (C), 105.2 (CH), 103.6 (C), 102.3 (CH), 101.7 (CH), 33.0 (CH_2); HRMS (EI+) *m*/*z* 308.0691 ($[M]^+$ $C_{18}H_{12}O_5$, requires 308.0684).

*4.1.20. 3-Allyl-2,9-dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**28**).* This white solid compound was prepared by the BBr_3 mediated demethylative cyclization of **24**, similar to that described for the preparation of **14**. Yield 74%; R_f 0.3 (1:4:12 methanol:ethyl acetate:hexane); mp 285–290 °C; ν_{max} (film) cm^{-1} 1686, 1555, 1415, 1245, 1101, 1025; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.06 (br s, 1H, OH), 7.66 (d, 1H, *J*=8.5 Hz, C7-H), 7.19 (s, 1H, C1-H), 7.15 (s, 1H, C10-H), 7.14 (s, 1H, C4-H), 6.92 (d, 1H, *J*=8.5 Hz, C8-H), 6.05–5.85 (m, 1H, C2′-H), 5.20–5.00 (m, 2H, C3′-H_2), 3.33 (d, 2H, *J*=6.0 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 158.3 (C), 157.5 (C), 157.4 (C), 156.2 (C), 152.0 (C), 146.1 (C), 135.8 (CH), 132.0 (C), 120.9 (CH), 117.7 (CH), 116.5 (CH_2), 114.6 (C), 114.2 (CH), 110.4 (C), 104.7 (C), 104.4 (CH), 98.6 (CH), 33.9 (CH_2); HRMS (EI+) *m*/*z* 308.0681 ($[M]^+$ $C_{18}H_{12}O_5$, requires 308.0685).

*4.1.21. 9-Hydroxy-2-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**29**).* Grubb's second-generation catalyst (3 mg, 0.0035 mmol) was added to a degassed solution of **25** (20 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) and 2-methyl-2-butene (2 mL). The solution was heated in a sealed tube at 100 °C for 15 min by a microwave reactor (Biotage Initiator 2.0, standard configuration, temperature control, external IR temperature sensor, fixed hold time). CH_2Cl_2 was removed in vacuum, and the mixture was purified by reverse phase semipreparative HPLC (symmetry C_{18}, 7 μm, solvent gradient 9:1 CH_3CN:H_2O) to get compound **29** (17 mg, 77%) as a white solid. R_f 0.4 (1:1 ethyl acetate:hexane); mp 110–112 °C; ν_{max} (film) cm^{-1} 1735, 1629, 1508, 1443, 1375, 1093; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.91 (d, 1H, *J*=8.0 Hz, C7-H), 7.73 (s, 1H, C1-H), 7.40–7.32 (m, 2H, C4-H & C3-H), 7.14 (s, 1H, C10-H), 6.97 (d, 1H, *J*=8.0 Hz, C8-H), 5.35 (t, 1H, *J*=6.0 Hz, C2′-H), 3.44 (d, 2H, *J*=6.0 Hz, C1′-H_2), 1.77 (s, 3H, CH_3), 1.75 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.7 (C), 158.8 (C), 156.9 (C), 156.3 (C), 151.8 (C), 138.8 (C), 133.9 (C), 131.9 (CH), 129.6 (CH), 122.4 (CH), 122.2 (CH), 120.6 (C), 117.5 (CH), 114.4 (C), 112.8 (CH), 106.1 (C), 99.2 (CH), 33.9 (CH_2), 26.0 (CH_3), 18.1 (CH_3); HRMS (EI+) *m*/*z* 320.1053 ($[M]^+$ $C_{20}H_{16}O_4$, requires 320.1049).

*4.1.22. 3-Hydroxy-2-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**30**).* This white solid compound was prepared by the Grubb's metathesis reaction of **26**, following the same procedure as described for the synthesis of **29**. Yield 72%; R_f 0.4 (1:1 ethyl acetate:hexane); mp 238–240 °C; ν_{max} (film) cm^{-1} 1719, 1635, 1418, 1260, 1141, 1007; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.92 (d, 1H, *J*=8.0 Hz, C7-H), 7.85 (d, 1H, *J*=8.0 Hz, C10-H), 7.69 (s, 1H, C1-H), 7.52–7.44 (m, 2H, C8-H & C9-H), 6.95 (s, 1H, C4-H), 5.37 (t, 1H, *J*=6.0 Hz, C2′-H), 3.33 (d, 2H, *J*=6.0 Hz, C1′-H_2), 1.75 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.7 (C), 159.8 (C), 157.6 (C), 154.5 (C), 153.6 (C), 132.6 (C), 126.7 (C), 126.1 (CH), 125.2 (CH), 123.2 (C), 121.6 (CH), 121.5 (CH), 120.3 (CH), 112.0 (CH), 103.4 (C), 102.5 (CH), 101.6 (C), 27.5 (CH_2), 25.6 (CH_3), 17.7 (CH_3); HRMS (EI+) *m*/*z* 320.1051 ($[M]^+$ $C_{20}H_{16}O_4$, requires 320.1048).

*4.1.23. 3,8-Dihydroxy-2-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**31**).* The Grubb's metathesis reaction for the synthesis of this compound from **27** is similar to that described for **29**. Yield 79%; R_f 0.5 (1:4:12 methanol:ethyl acetate:hexane); mp>360 °C, chars at 240 °C; ν_{max} (film) cm^{-1} 1718, 1630, 1426, 1268, 1163, 1005; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.72 (br s, 1H, OH), 7.63 (s, 1H, C1-H), 7.61 (d, 1H, *J*=9.0 Hz, C10-H), 7.24 (d, 1H, *J*=2.5 Hz, C7-H), 6.92 (s, 1H, C4-H), 6.88 (dd, 1H, *J*=9.0, 2.5 Hz, C9-H), 5.34 (t, 1H, *J*=8.0 Hz, C2′-H), 3.31 (d, 2H, *J*=8.0 Hz, C1′-H_2), 1.73 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.1 (C), 159.8 (C), 157.8 (C), 155.3 (C), 153.5 (C), 148.5 (C), 132.7 (C), 126.7 (C), 124.2 (CH), 121.7 (CH), 121.3 (CH), 114.2 (C), 112.4 (CH), 105.2 (CH), 103.6 (C), 102.5 (C), 101.7 (CH), 27.6 (CH_2), 25.7 (CH_3), 17.7 (CH_3); HRMS (EI+) *m*/*z* 336.0999 ($[M]^+$ $C_{20}H_{16}O_5$, requires 336.0997).

*4.1.24. 2,9-Dihydroxy-3-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**32**).* This white solid compound was produced by the Grubb's metathesis reaction of **28**, following the same procedure as described for the synthesis of **29**. Yield 82%; R_f 0.5 (1:4:12 methanol:ethyl acetate:hexane); mp>360 °C, chars at 230 °C; ν_{max} (film) cm^{-1} 1685, 1629, 1560, 1438, 1383, 1251, 1097; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.20 (br s, 1H, OH), 7.72 (d, 1H, *J*=8.0 Hz, C7-H), 7.25 (s, 1H, C1-H), 7.24 (s, 1H, C10-H), 7.21 (s, 1H, C4-H), 6.97 (d, 1H, *J*=8.0 Hz, C8-H), 5.32 (t, 1H, *J*=7.5 Hz, C2′-H), 3.33 (d, 2H, *J*=7.5 Hz, C1′-H_2), 1.72 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.0 (C), 158.1 (C), 157.9 (C), 156.7 (C), 152.6 (C), 146.7 (C), 134.1 (C), 133.4 (C), 121.7 (CH), 121.4 (CH), 117.8 (CH),

115.0 (C), 114.7 (CH), 110.6 (C), 105.0 (C), 104.8 (CH), 99.1 (CH), 28.8 (CH_2), 25.9 (CH_3), 19.5 (CH_3); HRMS (EI+) *m/z* 336.0995 ($[M]^+$ $C_{20}H_{16}O_5$, requires 336.0998).

*4.1.25. Methyl 2-(2,4,5-trimethoxyphenyl)acetate (**33**).*[15,24] A mixture of 2,4,5-trimethoxybenzaldehyde (4 g, 20.4 mmol), hippuric acid (4.38 g, 24.5 mmol), powdered fused sodium acetate (1.76 g, 21.42 mmol), and acetic anhydride (6.16 mL, 65.28 mmol) was heated on an oil bath at 120 °C. The mixture turned almost solid and then gradually liquefied (15–20 min). The temperature was decreased to 100 °C and allowed to stir for 3 h. The reaction was cool to room temperature; ethanol (50 mL) was added and allowed to stand overnight. The product was filtered by suction while washing with ice-cold alcohol (2×100 mL), hot water (2×100 mL) and dried to get a yellowish powder. 10% sodium hydroxide (20 mL) was added to this and refluxed for 10 h. After cooling, 40% NaOH (10 mL) was added and then 30% hydrogen peroxide (10 mL) diluted with water (20 mL) was added cautiously maintaining the temperature of the solution below 15 °C using an ice-salt bath. The solution was allowed to stand at room temperature for overnight and then acidified by the addition of conc. HCl. The acidic solution thus formed was extracted with benzene (2×100 mL), washed with water (2×40 mL), brine (40 mL) and dried (Na_2SO_4). Removal of the benzene produced brown oily compound which was dissolved in dry methanol (20 mL). Conc. H_2SO_4 (5 mL) was added and the mixture was refluxed for 4 h. Methanol was distilled off and the remaining solution was extracted with ethyl acetate (2×40 mL). The organic layer was washed with water (2×20 mL), brine (20 mL) and dried (Na_2SO_4). Concentration and silica gel column chromatographic purification produced **33** (3.2 g, 65%) as white solid. R_f 0.5 (1:3 ethyl acetate:hexane); mp 45–47 °C (lit.[24] 44–46 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72 (s, 1H, C6′-H), 6.51 (s, 1H, C3′-H), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 3.55 (s, 2H, C2-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7 (C), 151.9 (C), 149.1 (C), 143.1 (C), 114.9 (CH), 114.4 (C), 97.9 (CH), 56.8 (CH_3), 56.6 (CH_3), 56.3 (CH_3), 52.1 (CH_3), 35.2 (CH_2); HRMS (EI+) *m/z* 240.0993 ($[M]^+$ $C_{12}H_{16}O5$, requires 240.0998).

*4.1.26. Methyl 2,3,4-trimethoxyphenylacetate (**34**).*[25] This compound was obtained as colorless oil from 2,3,4-trimethoxybenzaldehyde (**34a**) using an identical procedure as followed for the preparation of compound **33**. Yield 58%; R_f 0.5 (1:3 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (d, 1H, *J*=8.5 Hz, C6′-H), 6.60 (d, 1H, *J*=8.5 Hz, C5′-H), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 3.56 (s, 2H, C2-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8 (C), 152.8 (C), 151.5 (C), 141.7 (C), 124.4 (CH), 120.2 (C), 106.7 (CH), 60.1 (CH_3), 60.0 (CH_3), 55.3 (CH_3), 51.2 (CH_3), 34.7 (CH_2); HRMS (EI+) *m/z* 240.0995 ($[M]^+$ $C_{12}H_{16}O5$, requires 240.0998).

*4.1.27. 5-Allyl-2,3,4-trimethoxybenzoic acid (**35**).* This white solid compound was obtained from 1-Allyl-5-bromo-2,3,4-trimethoxybenzene (See Supplementary data) following the similar procedure as described for the transformation of **7** to **9**. Yield 93%; R_f 0.3 (1:1 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1660, 1518, 1222, 1013; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (s, 1H, C6-H), 5.96–5.70 (m, 1H, C2′-H), 5.05–4.82 (m, 2H, C3′-H_2), 3.98 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.26 (d, 2H, *J*=6.0 Hz, C1′-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0 (C), 156.5 (C), 152.7 (C), 145.7 (C), 136.2 (CH), 130.0 (C), 127.7 (CH), 117.2 (C), 116.2 (CH_2), 62.3 (CH_3), 60.9 (CH_3), 60.8 (CH_3), 33.9 (CH_2); HRMS (EI+) *m/z* 252.0994 ($[M]^+$ $C_{13}H_{16}O_5$, requires 252.0998).

*4.1.28. Methyl 3-(5-allyl-2,4-dimethoxyphenyl)-3-oxo-2-(2,4,5-trimethoxyphenyl)propanoate (**36**).* This compound was obtained as yellowish oil from compound **33** and **19** following the similar procedure as described for the preparation of **12**. Yield 81%; R_f 0.4 (1:1 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1732, 1651, 1519, 1211, 1028; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (s, 1H, C6′-H), 6.70 (s, 1H, C6″-H), 6.50 (s, 1H, C3′-H), 6.31 (s, 1H, C3″-H), 5.96 (s, 1H, C2-H), 5.95–5.84 (m, 1H, C2‴-H), 5.02–4.94 (m, 2H, C3‴-H_2), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.25 (d, 2H, *J*=5.5 Hz, C1‴-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.8 (C), 170.5 (C), 162.1 (C), 159.4 (C), 151.1 (C), 148.8 (C), 142.4 (C), 136.1 (CH), 132.2 (CH), 120.7 (C), 118.0 (C), 115.1 (CH_2), 114.0 (C), 113.5 (CH), 96.9 (CH), 94.0 (CH), 56.7 (CH_3), 56.1 (CH_3), 55.9 (CH_3), 55.6 (CH_3), 55.1 (CH_3), 54.9 (CH_3), 51.7 (CH), 32.9 (CH_2); HRMS (EI+) *m/z* 444.1785 ($[M]^+$ $C_{24}H_{28}O_8$, requires 444.1784).

*4.1.29. Methyl 3-(5-allyl-2,3,4-trimethoxyphenyl)-2-(2,4-dimethoxyphenyl)-3-oxopropanoate (**37**).* This compound was obtained as yellowish oil from compound **35** and **11** following the identical procedure as described for the preparation of **12**. Yield 76%; R_f 0.4 (1:3 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1720, 1640, 1510, 1210, 1020; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (s, 1H, C6′-H), 7.10 (d, 1H, *J*=8.5 Hz, C6″-H), 6.43 (d, 1H, *J*=8.5 Hz, C5″-H), 6.42 (s, 1H, C3″-H), 5.93 (s, 1H, C2-H), 5.92–5.82 (m, 1H, C2‴-H), 5.05–4.95 (m, 2H, C3‴-H_2), 3.81 (s, 6H, OCH_3), 3.76 (s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H CO_2CH_3), 3.29 (d, 2H, *J*=6.5 Hz, C1‴-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.6 (C), 170.5 (C), 160.6 (C), 157.9 (C), 156.1 (C), 152.9 (C), 146.0 (C), 136.7 (CH), 130.5 (CH), 129.0 (C), 126.7 (C), 126.2 (CH), 116.1 (CH_2), 115.3 (C), 104.4 (CH), 98.8 (CH), 61.5 (CH_3), 61.0 (CH_3), 60.8 (CH_3), 56.5 (CH_3), 55.7 (CH_3), 55.5 (CH_3), 52.5 (CH), 34.1 (CH_2); HRMS (EI+) *m/z* 444.1780 ($[M]^+$ $C_{24}H_{28}O_8$, requires 444.1784).

*4.1.30. Methyl 3-(5-allyl-2,4-dimethoxyphenyl)-3-oxo-2-(2,3,4-trimethoxyphenyl)propanoate (**38**).* This yellowish oily compound was obtained from **34** and **19**, using an identical reaction sequence as described for the synthesis of **12**. Yield 83%; R_f 0.4 (1:1 ethyl acetate:hexane); ν_{max} (film) cm^{-1} 1738, 1651, 1604, 1468, 1270, 1096; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (s, 1H, C6′-H), 6.85 (d, 1H, *J*=8.5 Hz, C6″-H), 6.60 (d, 1H, *J*=8.5 Hz, C5″-H), 6.33 (s, 1H, C3′-H), 5.92 (s, 1H, C2-H), 5.92–5.85 (m, 1H, C2‴-H), 5.05–4.95 (m, 2H, C3‴-H_2), 3.85 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.71 (s, 3H, CO_2CH_3), 3.26 (d, 2H, *J*=6.0 Hz, C1‴-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 192.1 (C), 170.3 (C), 162.1 (C), 159.3 (C), 152.7 (C), 151.2 (C), 141.4 (C), 135.9 (CH), 132.0 (CH), 123.5 (C), 120.6 (CH), 120.4 (C), 117.7 (C), 115.0 (CH_2), 106.5 (CH), 94.0 (CH), 60.3 (CH_3), 60.0 (CH_3), 57.3 (CH_3), 55.2 (CH_3), 55.0 (CH_3), 54.8 (CH_3), 51.5 (CH), 32.8 (CH_2); HRMS (EI+) *m/z* 444.1780 ($[M]^+$ $C_{24}H_{28}O_8$, requires 444.1784).

*4.1.31. 2-Allyl-3,8,9-trihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**39**).* This brown solid compound was prepared by the BBr_3 mediated demethylative cyclization of **36**, similar to that described for the preparation of **14**. Yield 75%; R_f 0.3 (1:3:9 methanol:ethyl acetate:hexane); mp 340–342 °C; ν_{max} (film) cm^{-1} 1693, 1631, 1501, 1414, 1255, 1150, 1010; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.64 (br s, 1H, OH), 9.46 (br s, 1H, OH), 9.38 (br s, 1H, OH), 7.49 (s, 1H, C1-H), 7.21 (s, 1H, C7-H), 7.14 (s, 1H, C10-H), 6.84 (s, 1H, C4-H), 6.02–5.91 (m, 1H, C2′-H), 5.14–5.04 (m, 2H, C3′-H_2), 3.32 (d, 2H, *J*=6.5 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.0 (C), 158.5 (C), 157.8 (C), 152.7 (C), 148.8 (C), 145.6 (C), 144.4 (C), 136.2 (CH_2), 124.9 (C), 121.2 (C), 116.4 (CH), 114.2 (C), 104.9 (CH), 104.1 (C), 102.4 (CH), 102.2 (C), 99.0 (CH), 33.1 (CH_2); HRMS (EI+) *m/z* 324.0636 ($[M]^+$ $C_{18}H_{12}O_6$, requires 324.0634).

*4.1.32. 2-Allyl-3,4,9-trihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**40**).* This white solid compound was prepared by the BBr_3 mediated demethylative cyclization of **37**, following the same procedure

as described for the transformation of **12** to **14**. Yield 81%; R_f 0.3 (1:3:9 methanol:ethyl acetate:hexane); mp 258–260 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.03 (br s, 1H, OH), 9.99 (br s, 1H, OH), 9.69 (br s, 1H, OH), 7.68 (d, 1H, J=8.5 Hz, C7-H), 7.18 (s, 1H, C1-H), 7.15 (s, 1H, C10-H), 6.93 (d, 1H, J=8.5 Hz, C8-H), 6.10–5.90 (m, 1H, C2′-H), 5.18–5.00 (m, 2H, C3′-H_2), 3.39 (d, 1H, J=6.5 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.8 (C), 157.6 (C), 157.0 (C), 156.1 (C), 147.8 (C), 141.9 (C), 136.4 (CH), 132.4 (C), 124.9 (C), 120.7 (CH), 116.3 (CH_2), 114.8 (C), 114.0 (CH), 111.5 (CH), 104.1 (C), 102.0 (C), 98.7 (CH), 33.6 (CH_2); HRMS (EI+) m/z 324.0636 ([M]$^+$ $C_{18}H_{12}O_6$, requires 324.0634).

*4.1.33. 2-Allyl-3,9,10-trihydroxy-6H-benzofuro[3,2-c]chromen-6-one (**41**).* This white solid compound is the result of BBr_3 mediated demethylative cyclization of **38**, as described for the synthesis of **14**. Yield 82%; R_f 0.3 (1:3:9 methanol:ethyl acetate:hexane); mp>360 °C, chars at 232 °C; ν_{max} (film) cm^{-1} 1724, 1629, 1528, 1395, 1137, 1079; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.77 (br s, 1H, OH), 9.60 (br s, 1H, OH), 9.59 (br s, 1H, OH), 7.69 (s, 1H, C1-H), 7.16 (d, 1H, J=8.5 Hz, C7-H), 6.95 (d, 1H, J=8.5 Hz, C8-H), 6.94 (s, 1H, C4-H), 6.10–5.98 (m, 1H, C2′-H), 5.20–5.08 (m, 2H, C3′-H_2), 3.41 (d, 2H, J=7.0 Hz, C1′-H_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.6 (C), 158.8 (C), 157.9 (C), 153.0 (C), 144.9 (C), 144.8 (C), 144.7 (C), 136.2 (CH), 131.2 (C), 125.1 (C), 121.5 (CH), 116.6 (CH_2), 116.3 (C), 114.4 (CH), 109.8 (CH), 104.0 (C), 102.4 (CH), 33.1 (CH_2); HRMS (EI+) m/z 324.0633 ([M]$^+$ $C_{18}H_{12}O_6$, requires 324.0633).

*4.1.34. 2-Allyl-6-oxo-6H-benzofuro[3,2-c]chromene-3,8,9-triyl triacetate (**42**).* To a stirred solution of **39** (50 mg, 0.15 mmol) in CH_2Cl_2 (10 mL), triethyl amine (0.07 mL, 0.52 mmol), acetic anhydride (0.05 mL, 0.49 mmol), and DMAP (2 mg) was added. The reaction mixture was allowed to stir at room temperature for 6 h. After completion, as confirmed by TLC, water (10 mL) was added. The mixture was extracted with chloroform (40 mL) and the organic layer was washed with water (2×15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated. Chromatographic purification produced **42** (65 mg, 94%) as white solid. R_f 0.2 (1:3 ethyl acetate:hexane); mp 278–280 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (s, 1H, C1-H), 7.84 (s, 1H, C7-H), 7.55 (s, 1H, C10-H), 7.24 (s, 1H, C4-H), 6.00–5.85 (m, 1H, C2′-H), 5.25–5.05 (m, 2H, C3′-H_2), 3.40 (d, 2H, J=6.5 Hz, C1′-H_2), 2.35 (s, 3H, OAc), 2.34 (s, 6H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8 (C), 168.6 (C), 168.4 (C), 161.0 (C), 157.6 (C), 152.9 (C), 152.6 (C), 152.0 (C), 141.5 (C), 140.5 (C), 134.9 (C), 130.1 (C), 123.1 (CH), 121.6 (CH_2), 117.7 (C), 115.9 (CH), 112.2 (CH), 110.5 (C), 107.7 (CH), 105.5 (C), 34.4 (CH_2), 21.1 (CH_3), 20.9 (CH_3), 20.7 (CH_3); HRMS (EI+) m/z 450.0952 ([M]$^+$ $C_{24}H_{18}O_9$, requires 450.0951).

*4.1.35. 2-Allyl-6-oxo-6H-benzofuro[3,2-c]chromene-3,4,9-triyl triacetate (**43**).* This compound was obtained as white solid by the acetylation of **40** using an analogous procedure used during the synthesis of **42**. Yield 90%; R_f 0.6 (1:1 ethyl acetate:hexane); mp 232–234 °C; ν_{max} (film) cm^{-1} 1761, 1754, 1750, 1715, 1640, 1500, 1285; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (d, 1H, J=8.0 Hz, C7-H), 7.76 (s, 1H, C1-H), 7.47 (d, 1H, J=1.5 Hz, C10-H), 7.20 (dd, 1H, J=8.0, 1.5 Hz, C8-H), 5.98–5.85 (m, 1H, C2′-H), 5.25–5.10 (m, 2H, C3′-H_2), 3.41 (d, 2H, J=6.5 Hz, C1′-H_2), 2.42 (s, 3H, OAc), 2.35 (s, 6H, OAc); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4 (C), 167.6 (C), 167.3 (C), 159.9 (C), 156.6 (C), 155.5 (C), 149.8 (C), 145.2 (C), 144.4 (C), 134.5 (CH), 131.6 (C), 130.8 (C), 122.1 (CH), 121.0 (C), 119.7 (CH), 119.2 (CH), 118.0 (CH_2), 111.3 (C), 106.2 (CH), 105.5 (C), 34.5 (CH_2), 21.3 (CH_3), 20.5 (CH_3), 20.5 (CH_3); HRMS (EI+) m/z 450.0952 ([M]$^+$ $C_{24}H_{18}O_9$, requires 450.0951).

*4.1.36. 2-(3-Methylbut-2-en-1-yl)-6-oxo-6H-benzofuro[3,2-c]chromene-3,8,9-triyl triacetate (**44**).* Grubb's second-generation catalyst (4 mg, 0.004 mmol) was added to a degassed solution of **42** (30 mg, 0.07 mmol) in CH_2Cl_2 (10 mL) and 2-methyl-2-butene (3 mL). The mixture was allowed to stir at room temperature for 12 h. Once the reaction is complete, as checked by TLC, it was concentrated and purified by silica gel column chromatography to afford **44** (27 mg, 85%) as white solid. R_f 0.4 (1:3 ethyl acetate:hexane); mp 261–263 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (s, 1H, C1-H), 7.82 (s, 1H, C7-H), 7.57 (s, 1H, C10-H), 7.22 (s, 1H, C4-H), 5.26 (t, 1H, J=7.5 Hz, C2′-H), 3.33 (d, 2H, J=7.5 Hz, C1′-H_2), 2.35 (s, 3H, OAc), 2.33 (s, 6H, OAc), 1.79 (s, 3H, CH_3), 1.73 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8 (C), 168.6 (C), 168.4 (C), 161.1 (C), 157.8 (C), 152.7 (C), 152.6 (C), 152.1 (C), 141.5 (C), 140.5 (C), 134.9 (C), 131.7 (C), 122.7 (CH), 121.7 (C), 120.6 (CH), 115.9 (CH), 112.1 (CH), 110.5 (C), 107.7 (CH), 105.4 (C), 28.6 (CH_2), 26.0 (CH_3), 21.1 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 18.2 (CH_3); HRMS (EI+) m/z 478.1262 ([M]$^+$ $C_{26}H_{22}O_9$, requires 478.1264).

*4.1.37. 2-(3-Methylbut-2-en-1-yl)-6-oxo-6H-benzofuro[3,2-c]chromene-3,4,9-triyl triacetate (**45**).* This white solid powder like compound was prepared by a second generation Grubb's catalyzed olefin metathesis reaction of **43** following an identical procedure as described for the synthesis of **44**. Yield 84%; R_f 0.3 (1:3 ethyl acetate:hexane); mp 212–214 °C; ν_{max} (film) cm^{-1} 1765, 1760, 1755, 1710, 1629, 1490, 1280; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, 1H, J=8.5 Hz, C7-H), 7.71 (s, 1H, C1-H), 7.47 (d, 1H, J=1.5 Hz, C10-H), 7.18 (dd, 1H, J=8.5, 1.5 Hz, C8-H), 5.25 (t, 1H, J=7.0 Hz, C2′-H), 3.33 (d, 2H, J=7.0 Hz, C1′-H_2), 2.41 (s, 3H, OAc), 2.34 (s, 3H, OAc), 2.35 (s, 3H, OAc), 1.79 (s, 3H, CH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4 (C), 167.8 (C), 167.4 (C), 160.1 (C), 156.7 (C), 155.5 (C), 149.8 (C), 145.0 (C), 144.4 (C), 135.1 (C), 132.4 (C), 131.5 (C), 122.1 (CH), 121.2 (C), 120.2 (CH), 119.6 (CH), 118.9 (CH), 111.3 (C), 106.2 (CH), 105.5 (C), 28.7 (CH_2), 25.9 (CH_3), 21.3 (CH_3), 20.5 (CH_3), 20.5 (CH_3), 18.1 (CH_3); HRMS (EI+) m/z 478.1262 ([M]$^+$ $C_{26}H_{22}O_9$, requires 478.1264).

*4.1.38. 3,4,9-Trihydroxy-2-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**46**).* This colorless solid compound was synthesized in three steps from **40**, without purification of the intermediates, following an identical procedure as described for the synthesis of **2**. Yield 60% in three steps. R_f 0.5 (1:3:9 methanol:ethyl acetate:hexane); mp 250–252 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.03 (br s, 1H, OH), 9.95 (br s, 1H, OH), 9.66 (br s, 1H, OH), 7.70 (d, 1H, J=9.0 Hz, C7-H), 7.19 (s, 1H, C1-H), 7.18 (s, 1H, C10-H), 6.94 (d, 1H, J=9.0 Hz, C8-H), 5.34 (t, 1H, J=6.0 Hz, C2′-H), 3.33 (d, 2H, J=6.0 Hz, C1′-H_2), 1.73 (s, 3H, CH_3), 1.70 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.8 (C), 157.6 (C), 157.0 (C), 156.0 (C), 147.8 (C), 141.7 (C), 132.4 (C), 132.3 (C), 126.3 (C), 122.0 (C), 120.6 (CH), 114.7 (C), 113.9 (CH), 110.9 (CH), 104.0 (C), 101.9 (C), 98.7 (CH), 27.9 (CH_2), 25.6 (CH_3), 17.8 (CH_3); HRMS (EI+) m/z 352.0947 ([M]$^+$ $C_{20}H_{16}O_6$, requires 352.0946).

*4.1.39. 3,9,10-Trihydroxy-2-(3-methylbut-2-en-1-yl)-6H-benzofuro[3,2-c]chromen-6-one (**47**).* This white solid compound was prepared in three consecutive steps, starting from **41** as described for the synthesis of **2**. Yield 64% in three steps. R_f 0.5 (1:3:9 methanol:ethyl acetate:hexane); mp>360 °C, chars at 215 °C; ν_{max} (film) cm^{-1} 1718, 1629, 1508, 1383, 1264; ^{1}H NMR (Acetone-d_6, 500 MHz) δ 7.71 (s, 1H, C1-H), 7.28 (d, 1H, J=7.5 Hz, C7-H), 7.03 (d, 1H, J=7.5 Hz, C8-H), 6.96 (s, 1H, C4-H), 5.44 (t, 1H, J=6.5 Hz, C2′-H), 3.44 (d, 2H, J=6.5 Hz, C1′-H_2), 1.78 (s, 3H, CH_3), 1.77 (s, 3H, CH_3); ^{13}C NMR (Acetone -d_6, 125 MHz) δ 161.1 (C), 159.7 (C), 158.8 (C), 154.4 (C), 145.6 (C), 145.4 (C), 133.7 (C), 132.1 (C), 127.6 (C), 122.8 (CH), 122.3 (CH), 118.4 (C), 115.0 (CH), 111.5 (CH), 105.8 (C), 103.9 (C), 103.5 (CH), 28.6 (CH_2), 26.0 (CH_3), 18.0 (CH_3); HRMS (EI+) m/z 352.0946 ([M]$^+$ $C_{20}H_{16}O_6$, requires 352.0947).

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Supplementary data

Supplementary data (Supplementary data containing detailed experimental procedure and the characterization data of all the synthesized compounds (Supplementary data—Experimental) along with copies of ^{1}H and ^{13}C NMR (Supplementary data—NMR) can be found, in the online version) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.066.

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