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Original article

Synthesis and anti-cancer activity evaluation of novel prenylated and geranylated chalcone natural products and their analogs

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ABSTRACT

Four natural chalcones bearing prenyl or geranyl groups, i.e., bavachalcone (**1a**), xanthoangelol (**1b**), isobavachalcone (**1c**), and isoxanthoangelol (**1d**) were synthesized by using a regio-selective iodination and the Suzuki coupling reaction as key steps. The first total synthesis of isoxanthoangelol (**1d**) was achieved in 36% overall yield. A series of diprenylated and digeranylated chalcone analogs were also synthesized by alkylation, regio-selective iodination, aldol condensation, Suzuki coupling and [1,3]-sigmatropic rearrangement. The structures of the 11 new derivatives were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The anticancer activity of these new chalcone derivatives against human tumor cell line K562 were evaluated by MTT assay *in vitro*. SAR studies suggested that the 5′-prenylation/geranylation of the chalcones significantly enhance their cytotoxic activity. Among them, Bavachalcone (**1a**) displayed the most potent cytotoxic activity against K562 with IC_{50} value of 2.7 μM. The morphology changes and annexin-V/PI staining studies suggested that those chalcone derivatives inhibited the proliferation of K562 cells by inducing apoptosis.

1. Introduction

Chalcones containing prenyl or geranyl groups are an abundant subclass of flavonoids which are widely found in nature and display a variety of biological and pharmacological activities. Isobavachalcone (**1c**), first isolated from *Psoralea corylifolia* [1], showed antibacterial, antifungal, anticancer, anti-reverse transcriptase, antitubercular, and antioxidant activities [2–4]. Bavachalcone (**1a**), also isolated from *soraleaorylifolia* [1,5], was shown to display a significant inhibitory effect on baculovirus-expressed BACE-1 *in vitro* [6] as well as osteoclast differentiation [7]. These natural chalcones also exhibit extremely high α-glucosidase inhibitory activity [8]. Xanthoangelol (**1b**), isolated from fresh roots of *Angelica keiskei* [9], exhibits antibacterial activity against Gram-Positive pathogenic bacteria [10], antitumor-promoting activity and cytotoxicity against neuroblastoma cells, which induced apoptotic cell death via the mitochondrial pathway and had no cytotoxicity against normal cells [11]. The newly discovered compound **1d**, 2′, 4′, 4-trihydroxy- 5-geranyl chalcone, coined here as isoxanthoangelol, was isolated from the leaves of *Artocarpus communis*, and reported to possess anticancer activity in SW 872 human liposarcoma cells (Fig. 1) [12].

Due to their structural uniqueness and potent bioactivity, the synthesis of prenylated and geranylated chalcone natural products has attracted much attention in recent years. In 2010, Jung reported the first total synthesis of **1b** with a total yield of 16.8% starting from 4-dihydroxyacetophenone (**1**) [13]. Sugamoto subsequently finished the total synthesis of **1a**, **1b** and **1c** with 12.4%, 28.1% and 17.2% overall yield respectively [14]. All of these syntheses used O-alkylation followed by Claisen rearrangement as the key steps to

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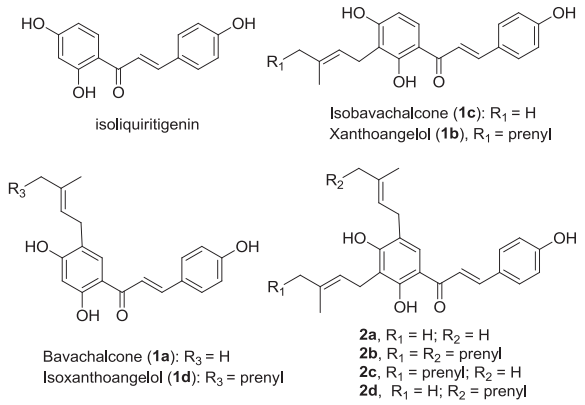


Fig. 1. The structures of chalcone natural products and their derivatives.

introduce the prenyl or geranyl groups. However, poor regioselectivity of the rearrangement limited their further use. Recently, McGlinchey applied iodination and Stille coupling to the synthesis of isobavachalocone. But the overall efficiency was low due to poor regiochemical control for the iodination as well as the low yield for the Stille coupling [15]. The 3′, 5′-diprenylated chalcone Medicagenin (**2a**) was isolated from the roots of *Crotalaria medicagenia* DC [16] and synthesized later by Narender [17] with a poor regioselectivity. However, no work has been reported on the synthesis and biological activity evaluation of other digeranylated chalcones, including **2b** and analogs **2c** and **2d**.

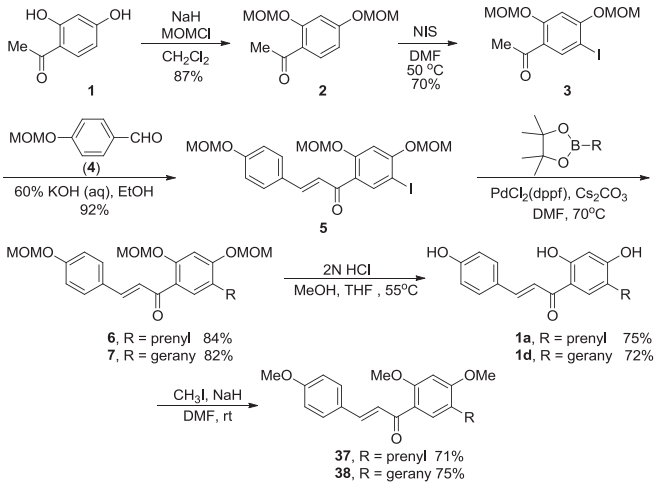
As part of our ongoing program on the synthesis of flavonoid and chalcone natural products, we have recently reported a regioselective iodination of flavonoids by NIS under neutral conditions [18], regioselective iodinations of chalcone derivatives using this protocol and the total synthesis of the aforementioned chalcone natural products by Suzuki coupling of the iodinated intermediates as the key step [19,20]. In this paper, we would like to report in details the synthesis and anticancer activity evaluation of the 3′ and/or 5′ prenylated/geranylated chalcone natural products (**1a**–**d**, **2a**) and their derivatives (**2b**–**d**, **33**–**40**) as well as the likely molecular mechanism of their cytotoxic activity.

2. Chemistry

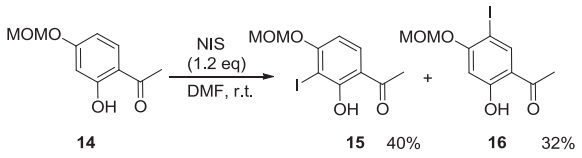
As shown in Scheme 1, iodide **3** was readily synthesized from the bis-MOM intermediate **2** by iodination of **1** with NIS in DMF [16]. Base promoted condensation of **3** with aldehyde **4** afforded the iodo precursor **5** which was converted into **6** and **7** by $PdCl_2$(dppf) catalyzed and microwave-assisted coupling reaction with the corresponding boronic acid pinacol esters in good yields. Removal of the MOM protecting groups finished the first total synthesis of isoxanthoangelol (**1d**) in 36% overall yield and the improved preparation of Bavachalcone (**1a**) in 35% overall yield respectively. The corresponding 2′, 4′, 4-trimethoxy derivatives **37** and **38** were obtained when **1a** and **1d** were treated with iodomethane and NaH in dry DMF in excellent yield.

The synthesis of isobavachalocone (**1c**) and xanthoganelol (**1b**) necessitates a 2-iodo-4-acetylresorcinol derivative such as **15** (Scheme 2). Unfortunately, iodination of the mono-MOM protected substrate **14** led to the formation of **15** along with a significant amount of its regioisomer **16**. However, utilization of an alternative iodination system (I_2/KIO_3) [21] provided a much cleaner access to the analogous iodide **8** directly from **1** (Scheme 3).

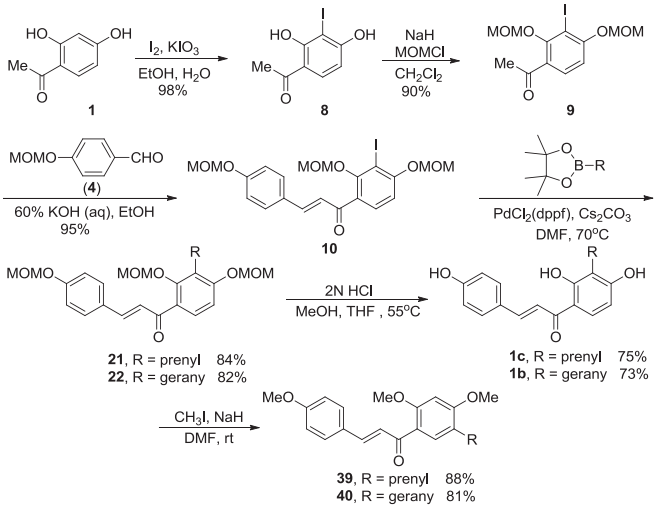
With compound **8** in hands, the total synthesis of both xanthoganelol **(1b)** and isobavachalocone **(1c)** was achieved uneventfully under similar conditions with an overall yield of 53% and 50%



Scheme 1. Synthetic route for target compounds **1a**, **1d**, **37** and **38**.



Scheme 2. Iodination of compound **14**.

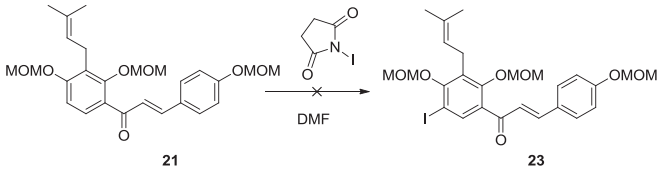


Scheme 3. Synthetic route for target compounds **1b**, **1c**, **39** and **40**.

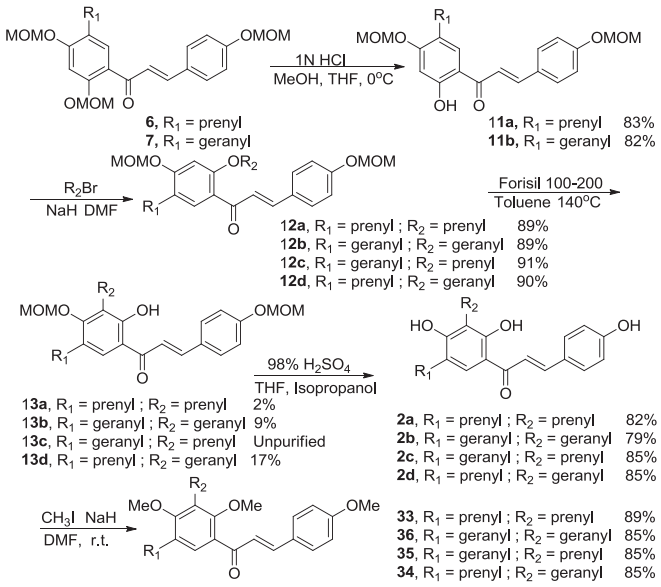
respectively, from the commercial material 4-acetylresorcinol (**1**). Compound **39** and **40** were prepared from **1b** and **1c** by methylation with MeI in 88% and 81% yield, respectively.

To synthesize the 3′, 5′-disubstituted chalcones Medicagenin (**2a**) and **2d**, we initially planned to employ the Pd-catalyzed coupling reaction to install the second prenyl/geranyl side-chain. This route required a 5′-iodo-3′- prenylated intermediate such as **23** (Scheme 4). Unfortunately, when using a protocol for the regieoselective iodination developed for the flavonoid substrates [18], the desired iodination product **23** was not formed. Therefore we decided to utilize the combination of Pd-catalyzed coupling reaction (for 5′-substitution) and O-alkylation/Claisen rearrangement (for 3′-substitution) to prepare the target compounds.

As shown in Scheme 5, compounds **6** and **7** were selectively deprotected with 1 M HCl at 0 °C to give the compounds **11a** and



Scheme 4. Iodination of compound **21**.



Scheme 5. Synthetic route for target compounds **2a**–**d** and **33**–**36**.

11b; the latter were treated with prenylbromide or geranylbromide under basic conditions to provide the alkylated products **12a**–**d**. The 1, 3′ rearrangement of these ethers were catalyzed by magnesium silicate (Florisil®,100–200 mesh) [22] at 140 °C in dry toluene to provide the desired compounds **13a**–**d**. Removal of the MOM protection groups was initially attempted with 3 M HCl at 60 °C, but the reaction only gave a low yield of the final target compounds **2a**–**d**. Deprotection of **13a**–**d** was finally achieved in 75–81% yield when 6% (v/v) of con. H_2SO_4 in THF and isopropanol at room temperature. To the best of our knowledge, this protocol of MOM deprotection has not been previously reported in the literature. The trimethoxy compounds **33**–**36** were prepared by methylation of **2a**–**d** with MeI in the presence of NaH in good yields.

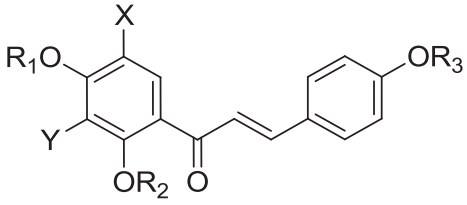
3. Results and discussion

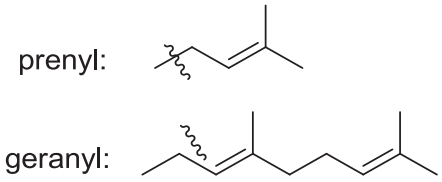
The *in vitro* antitumor activities of the newly synthesized prenyl and geranyl substituted chalcone natural products and their derivatives on human tumor cell K562 were evaluated by MTT assay with Camptothecin as the positive control.

As can be seen from the data in Table 1, that 5′-mono-substitution could significantly improve chalcone's cytotoxicity, as the 5′-prenylated chalcone Bavachalcone (**1a**) and 5′-geranylated chalcone Isoxanthoangelol (**1d**) exhibited the inhibitory potency against K562 at least 10 (for **1a**) and 7 times (for **1d**) stronger than their unsubstituted counterpart isoliquiritigenin itself, which suggested that the relatively large size and the hydrophobic nature of the substitution group at this position of the molecule could potentially become a key factor to improve the anticancer activity of the substituted chalcone derivatives.

The 3′-geranyl mono-substituted chalcone Xanthoangelol (**1b**) also showed good cytotoxic activity (3.98 μM). However, the

Table 1
Antitumor activities of chalcone derivatives *in vitro*.





No.	Entry	R_1	R_2	R_3	X	Y	IC_{50}(μM) K562	IC_{50}(μM) HUV-EC
1	1a	H	H	H	Prenyl	H	2.77 ± 1.07	39.73 ± 2.32
2	1b	H	H	H	H	Geranyl	3.98 ± 0.62	>100
3	1c	H	H	H	H	Prenyl	29.49 ± 2.26	>100
4	1d	H	H	H	Geranyl	H	4.33 ± 3.59	30.18 ± 1.28
5	2a	H	H	H	Prenyl	Prenyl	3.25 ± 0.23	20.26 ± 1.70
6	2b	H	H	H	Geranyl	Geranyl	31.65 ± 6.58	45.70 ± 12.70
7	2c	H	H	H	Geranyl	Prenyl	8.07 ± 4.98	35.31 ± 1.41
8	2d	H	H	H	Prenyl	Geranyl	10.65 ± 5.30	37.28 ± 1.24
9	33	CH_3	CH_3	CH_3	Prenyl	Prenyl	19.33 ± 1.24	36.33 ± 4.76
10	34	CH_3	CH_3	CH_3	Prenyl	Geranyl	17.53 ± 4.88	33.90 ± 2.56
11	35	CH_3	CH_3	CH_3	Geranyl	Prenyl	15.96 ± 4.32	37.72 ± 3.40
12	36	CH_3	CH_3	CH_3	Geranyl	Geranyl	21.62 ± 2.09	46.46 ± 1.96
13	37	CH_3	CH_3	CH_3	Prenyl	H	3.04 ± 0.38	45.58 ± 11.79
14	38	CH_3	CH_3	CH_3	Geranyl	H	4.64 ± 1.31	78.01 ± 1.87
15	39	CH_3	CH_3	CH_3	H	Prenyl	21.91 ± 4.4	54.76 ± 10.69
16	40	CH_3	CH_3	CH_3	H	Geranyl	9.58 ± 4.74	37.68 ± 4.67
17	Isoliquiritigein	H	H	H	H	H	29.27 ± 6.83	41.17 ± 1.48
18	Camptothecin						0.13 ± 0.04	0.20 ± 0.01

potency of it 3′-prenylated counterpart (**1c**) dropped by 7.5 folds against K562. Similar trend was noticed when the trimethoxyl 3′-geranylated compound **40** was compared to trimethoxyl 3′-prenylated compound **39**. This observation suggests that the good inhibitory activity of **1b** does not simply correlate with the hydrophobic nature of the geranyl group. The size and spatial orientation of the extra prenyl moiety (comparing to **1c**) may also play a role.

As shown in Table 1, the activity of the 3′, 5′-diprenylated chalcone **2a** (Medicagenin) against K562 (3.25 μM) was 9 time better than that of its mother chalcone (isoliquiritigenin). However, when one of the two prenyl groups in compound **2a** was replaced with geranyl moiety, namely for 5′-prenyl-3′-geranyl chalcones **2d** and **34**, 3′-prenyl-5′-geranyl chalcones **2c** and **35** as well as the 3′,5′-digeranylated chalcone **2b** and **36**, their potency dropped 2–6 folds from that of **2a**.

To examine the impact of the 2′, 4′, 4-trihydroxy groups on the 3′ or/and 5′-prenylated/geranylated chalcones' cytotoxic activity against K562, 8 novel trimethoxy 3′ or/and 5′ substituted chalcone derivatives were synthesized from their trihydroxy counterparts. The test results illustrated that the methoxy group did not enhance the potency. The trimethoxy 5′-prenylated/geranylated compounds (**37** and **38**) maintained a good inhibition, indicating that hydrogen bond donor of the hydroxyl groups in these 5′-substituted chalcones are not necessary for their activity and their 2′, 4′, 4 positions might tolerance certain size of O-linked substitution without sacrificing their potency. However, in the presence of a 3′-prenyl/geranyl moiety (**33**–**36**, **39** and **40**), the 2′, 4′, 4-trimethoxy groups did cause 2-7 folds activity drop from their trihydroxy counterparts. This observation suggested that the methoxy moieties at the 2′ and 4′ positions maybe too crowded for the 3′-substitution and therefore the 3′-prenyl/geranyl moiety might lose their favorite 3-dimentional orientation for the good inhibition.

To determine the cytotoxic activity on normal human cells, MTT assay was used for the evaluation of the cytotoxic potency of the target compounds against the human umbilical vein endothelial cell lines HUVEC. As compared to the cytotoxic potency to the K562 cells, all the targets compounds showed higher cell viability rate for HUVEC cells, which suggested that these compounds possessed low cytotoxicity to normal human cells HUVEC than to cancer cells K562 (Table 1).

In this study, the molecular mechanism of the cytotoxic activity of the chalcone derivatives with an IC_{50} value less than 5.0 μM was investigated on K562 cells. It was obvious that treatment with chalcone derivatives causes K562 cells' typical apoptotic morphology change, e.g. cell shrinkage and/or blebbing. As shown in Fig. 2A, the apoptotic cells were clearly observed in K562 cells after treatment with the chalcone derivatives for 48 h. Flow cytometic analysis also showed that apoptotic cells appeared in chalcone derivatives-treated K562 cells when double labelled with annexin-V-FITC and PI (Fig. 2B). After treatment with the chalcone derivatives, the apoptotic rates (Annexin V^+/PI^-) of K562 cells were increased to at least 37.5% of the total cells whereas only 5.0% cells were observed as apoptotic cells in the control. Taken together, these results suggested that the chalcone derivatives inhibited the

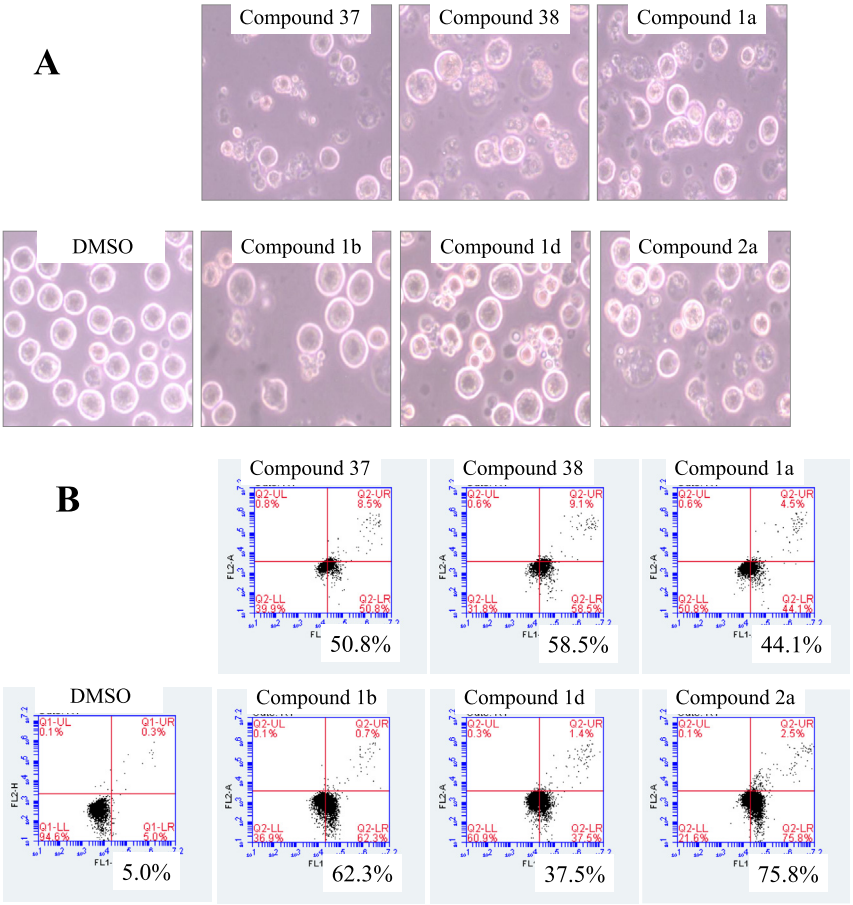


Fig. 2. Chalcone derivatives induced apoptosis in K562 cells. (A) Morphological changes induced by chalcone derivatives (30 μM) treatment for 48 h were observed. (B) Chalcone derivatives-treated K562 cells were labeled with Annexin-V-FITC and PI and apoptosis was determined using FACS analysis. Data was shown as the mean of three independent experiments. The cell percentage in each area was indicated.

proliferation of K562 cells by inducing apoptosis.

4. Conclusions

In summary, the first total synthesis of isoxanthoangelol (**1d**) was accomplished in 5 steps and 36% overall yield. The improved synthesis of bavachalcone (**1a**), xanthoangelol (**1b**) and isobavachalcone (**1c**) as well as the preparation of a series of novel 3′ or/and 5′ prenylated/geranylated chalcone derivatives were accomplished. The anticancer activity of the 16 newly synthesized chalcone derivatives against human tumor cell line K562 were evaluated and the test result illustrated that the 5′-prenylation/geranylation of the chalcones could significantly enhance their cytotoxic activity and the 3′-geranyl mono-substituted chalcone Xanthoangelol (**1b**) also showed good cytotoxic activity (3.98 μM). However, the introduce of another prenyl/geranyl groups and/or the 2′, 4′, 4-trimethoxy groups did not further improve the activity. Moreover, the molecular mechanism of the cytotoxic activity of 6 chalcone derivatives were also investigated on K562 cells and the results suggested that chalcone derivatives inhibited the proliferation of K562 cells by inducing apoptosis. Further optimization of the structure to improve the bioavailability and solubility is ongoing.

5. Experimental section

5.1. Chemistry

All chemicals (reagent grade) used were purchased from Sigma-Aldrich (U.S.A) and Aladdin-Reagent Co., Ltd (China). The solvents for reaction were distilled over Na (for toluene and THF) or CaH_2 (for CH_2Cl_2) under a nitrogen atmosphere. All reactions were carried out in oven-dried glassware under an inert atmosphere (nitrogen or argon). Microwave reaction was carried out in Biotage Initiator made in Sweden. TLC was run on the silica gel coated aluminum sheets (Silica Gel 60GF254, E. Merck, Germany). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AVANCE instrument (400 MHz). ESI mass spectra were obtained on an LCQ-Advantayc-MAX (LAM10188, Finnigan, Co., Ltd, USA). The purity of the final products was determined by HPLC (LabTech) on a Diamonsil C_{18} column (4.6 mm × 250 mm, 5 μm) with methanol/H_2O (90/10 v/v) at 0.5 mL/min flow rate and 254 nm detector wavelength.

5.1.1. 1-(2,4-bis(methoxymethoxy)phenyl)ethanone (**2**)

To a stirred solution of 1-(2,4-dihydroxyphenyl)ethanone (152.00 mg, 1.00 mmol) and anhydrous NaH (96.00 mg, 4.00 mmol) in dry Dichloromethane (5.00 mL) was slowly added chloromethyl methyl ether (483.00 mg, 6.00 mmol) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **2** (210.00 mg, 87%) as a white solid; ^{1}H and ^{13}C NMR identical with literature data [24]; LRMS (ESI) *m/z*: 263.09 $[M+Na]^+$.

5.1.2. 5-iodo-2,4-bis(methoxymethoxy)phenyl)ethanone (**3**)

To a solution of compound **2** (0.24 g, 1.00 mmol) in dry DMF (4 mL), was added NIS (0.27 g, 1.20 mmol), after the addition, the mixture was stirred at 70 °C for 10 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), and the mixture was poured into saturated sodium bicarbonate solution (10 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography to afford compound **3** (0.26 g, 70%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.51 (s, 6H), 5.27 (s, 2H), 5.28 (s, 2H), 6.91 (s, 1H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.7, 56.7, 56.7, 94.7, 94.9, 101.3, 124.1, 141.0, 158.6, 160.0, 196.6; HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}IO_5Na$ $[M+Na]^+$ 388.9862; found: 388.9859.

5.1.3. (E)-1-(5-iodo-2,4-bis(methoxymethoxy)phenyl)-3-(4(methoxymethoxy)phenyl)prop-2-en-1-one (**5**)

To a stirred solution of compound **3** (366.00 mg, 1.00 mmol) and 4-(methoxymethoxy)benzaldehyde (174.41 mg, 1.05 mmol) in ethanol (5 mL) was slowly added 60% KOH (2 mL) at 0 °C, then the reaction mixture was warm to room temperature and stirred for 12 h. After completion of reaction, the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with saturated sodium chloride solution, dried over sodium sulfate, filtrated, and concentrated under vacuum to get a reside which was recrystallized from ethyl acetate to afford compound **5** (475.00 mg, 92%) as a yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.50 (s, 6H), 3.55 (s, 3H), 5.23 (s, 2H), 5.26 (s, 2H), 5.31 (s, 2H), 6.96 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 16 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 16 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 56.7, 56.7, 94.2, 95.0, 95.2, 102.2, 116.5, 124.7, 125.9, 128.8, 130.0, 140.7, 143.1, 157.6, 159.1, 159.3, 190.0; HRMS (ESI) *m/z* Calcd for $C_{21}H_{23}IO_7Na$ $[M+Na]^+$ 537.0386; found: 537.0378.

5.1.4. (E)-1-(2,4-bis(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**6**)

To a stirred solution of compound **5** (514.00 mg, 1.00 mmol) and 3-Methyl-2-butenylboronic acid pinacol ester (235.00 mg, 1.20 mmol) in anhydrous DMF (3 mL) was added $PdCl_2$(dppf) (36.60 mg, 0.05 mmol, 0.05 equiv), Cesium carbonate (456.00 mg, 1.40 mmol). The mixture was heated at 70 °C by microwave for 2 h. The reaction mixture was cooled and monitored by TLC. After completion of the reaction, the reaction mixture was filtrated and evaporated under vacuum. The residue was purified by silica gel column chromatography to afford compound **6** (384.00 mg, 84%) as yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.71 (s, 6H), 3.29 (d, J = 7.6 Hz 2H), 3.48 (d, 9H), 5.21 (d, 4H), 5.25 (s, 3H), 6.90 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 15.6 Hz, 1H), 7.52 (m, 3H), 7.62 (d, J = 15.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 25.8, 28.1, 56.2, 56.3, 56.6, 94.2, 94.3, 95.5, 101.7, 116.5, 122.2, 123.7, 124.7, 125.5, 129.2, 129.9, 131.5, 132.6, 142.0, 155.8, 158.5, 158.8, 191.4; HRMS (ESI) *m/z* Calcd for $C_{26}H_{32}O_7Na$ $[M+Na]^+$ 479.2046; found: 479.2043.

5.1.5. Bavachalocone (***1a***)

To a solution of compound **6** (100.00 mg, 0.22 mmol) in MeOH (2 mL), was added 1N aqueous hydrochloric acid (1 mL) at 0 °C. The reaction mixture was heated to 50 °C for 6 h. The reaction was cooled to room temperature and MeOH was removed in vacuo. Ethyl acetate (10 mL) was then added and the layers were separated. The aqueous layer was extracted with Ethyl acetate (2x10 mL) and the combined organic layers were dried $MgSO_4$ concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel (eluant:n-hexane/EtOAc = 15:1) to afford Bavachalocone **(1a)** (53.00 mg, 75%, Purity: 97%) as a yellow solid: ^{1}H and ^{13}C NMR identical with literature data [1]; LRMS (ESI) *m/z* 325 $[M+H]^+$

5.1.6. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-bis(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**7**)

To a stirred solution **o**f compound **5** (514.00 mg, 1.00 mmol) and geranylboronic acid pinacol ester (317.00 mg, 1.20 mmol) in

anhydrous DMF (3 mL) was added $PdCl_2$(dppf) (36.60 mg, 0.05 mmol), Cesium carbonate (456.00 mg, 1.40 mmol). The mixture was heated at 70 °C by microwave for 2 h. The reaction mixture was cooled and monitored by TLC. After completion of the reaction, the reaction mixture was filtrated and evaporated under vacuum. The residue was purified by silica gel column chromatography to afford compound **7** (431.00 mg, 82%) as yellow oil; ^{1}H NMR (DMSO-d_6,400 MHz): δ 1.53 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 2.04 (m, 4H), 3.25 (d, J = 7.2 Hz, 2H), 3.36 (s, 3H), 3.39 (s, 3H), 3.41 (s, 3H), 5.07 (t, J = 16.8 Hz, 1H), 5.25 (m, 3H), 5.28 (s, 2H), 5.31 (s, 2H), 6.89 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 16 Hz, 1H), 7.51 (d, J = 16 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6):δ 16.2, 17.7, 25.7, 26.7, 28.0, 39.8, 56.1, 56.3, 56.6, 94.2, 94.3, 95.5, 101.7, 116.5, 122.1, 122.8, 123.7, 124.3, 124.8, 125.5, 129.2, 129.8, 131.4, 131.5, 136.2, 142.1, 155.8, 158.6, 158.8, 191.4; HRMS (ESI) *m*/*z* Calcd for $C_{31}H_{40}O_7Na$ [M+Na]$^+$ 547.2672; found: 547.2669.

5.1.7. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxyphenyl)-3-(4hydroxyphenyl)prop-2-en-1-one (**1d**)

The procedure is the same as the preparation of Bavachalocone by using compound 7 (100.00 mg, 0.19 mmol) as substrate to give compound **1d** (55.00 mg, 73%, purity: 100%) as a yellow solid. ^{1}H and ^{13}C NMR identical with literature data [12]; LRMS (ESI) *m*/*z* 392 [M+H]$^+$

5.1.8. (E)-1-(2,4-dimethoxy-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**37**)

Compound **37** A mixture of compound **1a** (0.10 g, 1 equiv), anhydrous NaH (0.05 g, 4 equiv), and CH_3I (dropwise addition of 0.15 g, 3.5 equiv) was stirred in DMF (3 mL) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **37** (80.00 mg, 71%, purity: 95%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (s, 3H), 1.72 (s, 3H), 3.29 (d, J = 7.2 Hz 2H), 3.84 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.27 (t, J = 7.2 Hz 1H), 6.45 (s, 1H), 6.91 (d, J = 4.8 Hz, 2H), 7.26 (s, 1H), 7.40 (d, J = 15.6 Hz,1H), 7.54 (d, J = 10.4 Hz, 3H), 7.64 (d, J = 16 Hz,1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.8, 25.8, 27.7, 55.4, 55.6, 56.1, 95.0, 114.3, 121.4, 122.3, 122.7, 125.2, 128.3, 129.9, 131.9, 132.6, 141.7, 158.9, 161.2, 161.5, 190.8; HRMS (ESI) *m*/*z* Calcd for$C_{23}H_{26}O_4Na$ [M+Na]$^+$ 389.1729; found: 389.1725.

5.1.9. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one 4 (**38**)

The procedure is the same as the preparation of compound **37** by using compound **1d** (480.00 mg, 0.19 mmol) as substrate to give compound **38** (400.00 mg, 75%, purity: 98%) as a yellow oil. ^{1}H NMR ($CDCl_3$,400 MHz): δ 1.60 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 2.15 (m, 4H), 3.35 (d, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.10 (m, 1H), 5.33 (t, J = 6.8 Hz, 1H), 6.42 (s, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.83 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6):δ 16.1, 17.7, 25.7, 26.7, 27.6, 39.8, 55.4, 55.6, 56.2, 95.0, 114.3, 121.4, 122.2, 122.8, 124.3, 125.2, 128.3, 129.9, 131.3, 131.6, 131.9, 136.2, 141.8, 158.9, 161.2, 161.5, 190.8. HRMS (ESI) *m*/*z* Calcd for $C_{28}H_{34}O_4Na$ [M+Na]$^+$ 457.2355; found: 457.2368.

5.1.10. 1-(2,4-Dihydroxy-3-iodophenyl)ethanone (**8**)

To a solution of 2,4-Dihydroxyacetophenone(10.00 g, 65.73 mmol) in ethanol (50 mL) and water (80 mL) was added iodine(7.51 g, 29.59 mmol) and potassium iodate (2.81 g, 13.13 mmol) at room temperature. The reaction was stirred vigorously overnignt. Then the mixture was diluted with water, extracted with ethyl acetate (3 × 100 mL), the combine the organic layers was washed with brine dry over sodium sulfate, filtered and concentrated under reduced pressure to provide the compound **8** (18.00 g, 98%) as offwhite solid. ^{1}H and ^{13}C NMR identical with literature data [21]; LRMS (ESI) *m*/*z* 277 [M+H]$^+$

5.1.11. 1-(3-Iodo-2,4-bis(methoxymethoxy)phenyl)ethanone (**9**)

To a stirred solution of compound **8** (278.00 mg, 1.00 mmol) and anhydrous NaH (96.00 mg, 4.00 mmol) in dry Dichloromethane (5 mL) was slowly added chloromethyl methyl ether (483.00 mg, 6.00 mmol) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **9** (330.00 mg, 90%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H), 3.51 (s, 3H), 3.56 (s, 3H), 5.07 (s, 2H), 5.30 (s, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.2, 56.6, 58.6, 87.0, 94.9, 101.2, 110.1, 129.0, 131.0, 157.1, 160.1, 198.6; HRMS (ESI) *m*/*z* Calcd for $C_{12}H_{15}I_1O_5Na$ [M+Na]$^+$ 388.9862; found: 388.9854.

5.1.12. (E)-1-(3-iodo-2,4-bis(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**10**)

The procedure is the same as the preparation of compound **5** by using compound **9** (100.00 mg, 0.27 mmol) as substrate to give compound **10**(134.00 mg, 95%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.48 (s, 3H), 3.51 (s, 3H), 3.53 (s, 3H), 5.03 (s, 2H), 5.21 (s, 2H), 5.31 (s, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 20.4 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.2, 56.6, 58.8, 86.8, 94.2, 94.9, 101.4, 110.3, 116.5, 124.3, 128.5, 129.2, 130.2, 131.5, 143.7, 157.1, 159.2, 159.8, 190.9; HRMS (ESI) *m*/*z* Calcd for $C_{21}H_{23}I_1O_7Na$ [M+Na]$^+$ 537.0386; found: 537.0382.

5.1.13. (E)-1-(2,4-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**21**)

The procedure is the same as the preparation of compound **6** by using compound **10** (100.00 mg, 0.19 mmol) as substrate to give compound **21** (75.00 mg, 84%), as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (s, 3H), 1.80 (s, 3H), 3.45 (s, 3H), 3.46 (d, 2H),3.48 (s, 3H), 3.48 (s, 3H), 4.92 (s, 2H), 5.21 (s, 2H), 5.23 (m, 1H), 5.25 (s, 2H), 6.94 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 16.8 Hz, 1H),7.47 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 23.4, 25.8, 56.2, 57.9, 94.0, 94.1, 101.3, 109.5, 116.5, 122.6, 124.8, 124.9, 128.1, 128.7, 128.8, 130.1, 131.7, 143.2, 155.5, 158.6, 159.1, 192.2; HRMS (ESI) *m*/*z* Calcd for $C_{26}H_{32}O_7Na$ [M+Na]$^+$ 479.2046; found: 479.2043;

5.1.14. (E)-1-(3-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-bis(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**22**)

The procedure is the same as the preparation of compound **21** by using compound **10** (100.00 mg, 0.19 mmol) as substrate to give compound **22** (84.00 mg, 82%), as yellow oil; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.52 (s, 3H), 1.59 (d, J = 5.6 Hz, 3H), 1.77 (s, 3H), 1.95 (t, J = 6.8 Hz, 2H), 2.01 (t, J = 7.2 Hz, 2H), 3.34 (s, 2H), 3.36 (s, 3H), 3.38 (s, 3H), 3.39 (s, 3H), 4.86 (s, 2H), 5.03 (t, J = 6.4 Hz, 1H), 5.17 (t, *J* = 16 Hz, 1H), 5.25 (s, 2H), 5.31 (s, 2H), 6.98 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 16 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 16.5, 18.0, 23.4, 25.9, 26.5, 56.2, 56.2, 57.7, 94.1, 94.1, 101.1, 109.9, 116.9, 122.8, 124.5, 124.6, 124.9, 128.0, 128.6, 128.9, 130.7, 131.2, 135.1, 143.1, 155.3, 158.4, 159.1, 191.3; HRMS (ESI) *m*/*z*

Calcd for $C_{31}H_{40}O_7Na$ $[M+Na]^+$ 547.2672; found: 547.2669.

*5.1.15. Isobavachalcone (**1c**)*

The procedure is the same as the preparation of Bavachalocone by using compound **21** (100.00 mg, 0.22 mmol) as substrate to give compound **1c** (53.00 mg, 75%, purity: 98%), as yellow powder. ^1H and ^{13}C NMR identical with literature data [1]; HRMS (ESI) *m/z* Calcd for $C_{20}H_{20}O_4$ $[M+H]^+$ 324.1362; found:324.1365.

*5.1.16. Xanthoangelol (**1b**)*

The procedure is the same as the preparation of Bavachalocone by using compound **22** (100.00 mg, 0.19 mmol) as substrate to give compound **1b** (54.00 mg, 72%, purity: 98%), as yellow powder. ^1H, ^{13}C NMR and EIMS identical with literature data [9].

*5.1.17. (E)-1-(2,4-dimethoxy-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**39**)*

The procedure is the same as the preparation of compound **37** by using compound **1c** (100.00 mg, 0.19 mmol) as substrate to give compound **39** (100.00 mg, 88%, purity: 98%), as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.69 (s, 3H), 1.79 (s, 3H), 3.40 (d, J = 6.8 Hz 2H), 3.70 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 5.19 (t, J = 6.8 Hz 1H), 6.72 (d, J = 8.4 Hz 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 16 Hz, 1H), 7.58 (m,3H), 7.69 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 22.8, 25.8, 55.4, 55.8, 63.1, 106.3, 114.4, 122.7, 123.9, 24.1, 126.3, 127.9, 129.6, 130.2, 131.6, 143.1, 158.9, 161.4, 161.4, 191.7; HRMS(ESI) *m/z* Calcd for $C_{23}H_{26}O_4Na$ $[M+Na]^+$ 389.1729; found: 389.1726;

*5.1.18. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**40**)*

The procedure is the same as the preparation of compound **39** by using compound **1b** (100.00 mg, 0.19 mmol) as substrate to give compound **40** (90.00 mg, 81%, purity: 95%), as yellow oil. ^1H NMR($CDCl_3$, 400 MHz): δ 1.60 (s, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 2.15 (m, 4H), 3.41 (d, J = 6.8 Hz, 2H), 3.69 (s, 3H),3.84 (s, 3H), 3.88 (s, 3H), 5.18 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 15.6 Hz, 1H), 7.58 (m, 3H), 7.69 (d, J = 16 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6):δ 16.1, 17.7, 25.7, 26.7, 27.6, 39.8, 55.4, 55.6, 56.2, 95.0, 114.3, 121.4, 122.2, 122.8, 124.3, 125.2, 128.3, 129.9, 131.3, 131.6, 131.9, 136.2, 141.8, 158.9, 161.2, 161.5, 190.8. HRMS (ESI) *m/z* Calcd for $C_{28}H_{34}O_4Na$ $[M+Na]^+$ 457.2355; found: 457.2355.

*5.1.19. (E)-1-(2-hydroxy-4-(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**11a**)*

To a solution of compound **6** (100.00 mg, 0.22 mmol) in MeOH (2 mL), was added 1N aqueous hydrochloric acid (1 mL) at 0 °C. The reaction was cooled to r.t and MeOH was removed in vacuo. Ethyl acetate (10 mL) was then added and the layers were separated. The aqueous layer was extracted with Ethyl acetate (2x10 mL) and the combined organic layers were dried $MgSO_4$ concentrated in vacuo to give a residue which was purified by flash chromatography on silica gel(eluant:n-hexane/EtOAc = 15:1) to afford Compound **11a** (75.00 mg, 83%) as a yellow solid, ^1H NMR and EIMS identical to literature data [9].

*5.1.20. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**11b**)*

The procedure is the same as the preparation of Compound **11a** by using compound **7** (100.00 mg, 0.22 mmol) as substrate to give compound **11b** (75.00 mg, 82%), as yellow solid, ^1H NMR and EIMS identical to literature data [9].

*5.1.21. (E)-1-(2-(((Z)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-4-(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**12d**)*

To a stirred solution of Compound **11a** (412.00 mg, 1.00 mmol) and NaH (52.00 mg, 1.30 mmol) in dry DMF (5 mL) was slowly added Geranylbromide (282.00 mg, 1.30 mmol) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **12d** (500.00 mg, 90%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.58 (s, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6.72 (s, 1H), 5.50 (t, J = 6.2 Hz, 1H), 5.31–5.24 (m, 1H), 5.24 (s, 2H), 5.13 (s,2H), 5.05 (m, 1H), 4.62 (d, J = 6.7 Hz, 2H), 3.50 (s, 3H), 3.48 (s, 3H), 3.28 (d, J = 7.3 Hz, 2H), 2.13–2.00 (m, 4H), 1.72 (m, 9H), 1.64 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 159.1, 158.6, 158.2, 141.8, 141.1, 132.4, 132.2, 131.9, 129.8, 129.6, 125.9, 123.7, 123.3, 122.7, 122.4, 119.1, 116.4, 99.5, 94.2, 66.0, 56.1, 39.5, 28.1, 26.3, 25.8, 25.6, 17.8, 17.7, 16.8. HRMS (ESI) *m/z* Calcd for $C_{34}H_{44}O_6H$ $[M+H]^+$ 549.3216; found: 549.3138.

*5.1.22. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2-(((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-4-(methoxymethoxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**12b**)*

To a stirred solution of compound **11b** (480.00 mg, 1.00 mmol) and NaH (52.00 mg, 1.30 mmol) in dry DMF (5 mL) was slowly added Geranylbromide (282.00 mg, 1.30 mmol) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **12b** (550.00 mg, 89%) as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 3.3 Hz, 2H), 7.58 (d, J = 1.7 Hz, 2H), 7.53 (dd, J = 9.0, 5.3 Hz, 1H), 7.06–6.95 (m, 2H), 6.73 (s, 1H), 5.51 (d, J = 6.6 Hz, 1H), 5.29 (t, J = 7.2 Hz, 1H), 5.25 (s, 2H), 5.20 (s, 2H), 5.07 (m, 2H), 4.62 (d, J = 6.6 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 3H),3.30 (d, J = 7.2 Hz, 2H), 2.18–1.91 (m, 8H), 1.72 (m, 6H), 1.66 (m, 6H), 1.60–1.52 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 159.1, 158.6, 158.1, 141.8, 141.1, 135.9, 132.2, 131.8, 131.4, 129.8, 129.6, 125.9, 124.3, 123.7, 123.4, 122.7, 122.3, 119.1, 116.4, 99.5, 94.2, 66.0, 56.1, 39.8, 39.5, 32.0, 28.0, 26.7, 26.6, 26.3, 25.7, 25.6, 23.5, 17.7, 16.8, 16.2. HRMS (ESI) *m/z* Calcd for $C_{39}H_{53}O_6$ $[M+H]^+$ 617.3842; found:. 617.3852.

*5.1.23. (E)-1-(4-(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)-2-((3-methylbut-2-en-1-yl)oxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**12a**)*

The procedure is the same as the preparation of compound **12d** by using compound **11a** (480 mg, 0.19 mmol) as substrate to give compound **12a** (500 mg, 89%) as a yellow oil. ^1H NMR and EIMS identical to literature data [23].

*5.1.24. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-4-(methoxymethoxy)-2-((3-methylbut-2-en-1-yl)oxy)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**12c**)*

The procedure is the same as the preparation of compound **12b** by using compound **11b** (480.00 mg, 0.190 mmol) as substrate to give compound **12c** (500.00 mg, 91%) as a yellow oil.^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.7 Hz, 2H), 7.59 (s, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 6.73 (s, 1H), 5.56–5.45 (m, 1H), 5.36–5.27 (m, 1H), 5.26 (s, 2H), 5.21 (s, 2H), 5.18–5.13 (m, 1H), 5.09 (m, 1H), 4.59 (d, J = 6.8 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 3.30 (d, J = 7.2 Hz, 2H), 2.06 (m, 4H), 1.77 (s, 3H), 1.73 (m, 6H), 1.66 (s,

3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.42, 159.1, 158.6, 158.2, 141.1, 138.6, 135.9, 132.2, 129.8, 126.1, 124.3, 123.4, 122.3, 119.4, 116.4, 94.3, 94.3, 65.9, 56.1, 39.8, 28.03, 26.72, 25.8, 25.7, 18.3, 17.7, 16.2. HRMS (ESI) *m/z* Calcd for $C_{34}H_{44}O_6H$ $[M+H]^+$ 549.3216; found:549.3222.

*5.1.25. (E)-1-(2-hydroxy-4-(methoxymethoxy)-3,5-bis(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**13a**)*

To a stirred solution of compound **12a** (3.00 g, 7.27 mmol) in dry toluene (15 mL) was slowly added 100–200 mesh Forisil® at room temperature, then the reaction mixture was string at 140 °C for 4 h, After completion of reaction, the reaction mixture was concentrated under vacuum to get a reside which was purified by silica gel column chromatography to afford compound **13a** (60.00 mg, 2%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.28 (s, 1H), 7.86 (d, J = 15.5 Hz, 1H), 7.64–7.55 (m, 3H), 7.47 (d, J = 15.4 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 5.32 (t, J = 7.0 Hz, 1H), 5.28–5.24 (m, 1H), 5.23 (s, 2H), 5.02 (s, 2H), 3.61 (s, 3H), 3.50 (s, 3H), 3.42 (d, J = 6.4 Hz, 2H), 3.38 (d, J = 7.0 Hz,2H), 1.79 (s, 6H), 1.75 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 162.2, 160.5, 159.4, 144.3133.1, 128.6, 128.1, 125.6, 123.7, 122.8, 122.4, 118.7, 116.8, 116.6, 99.9, 94.2, 57.7, 56.2, 28.5, 25.8, 25.7, 23.4, 18.0. HRMS (ESI) *m/z* Calcd for $C_{29}H_{37}O_6$ $[M+H]^+$ 481.2590; found: 481.2599.

*5.1.26. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-3-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-(methoxymethoxy) phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**13b**)*

To a stirred solution of compound **12b** (617.00 mg, 1 mmol) in dry toluene (15 mL) was slowly added 100–200 mesh Forisil® at room temperature, then the reaction mixture was string at 140 °C for 4 h, After completion of reaction, the reaction mixture was concentrated under vaccum to get a reside which was purified by silica gel column chromategraphy to afford compound **13b** (60.00 mg, 9%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.28 (d, J = 10.8 Hz, 1H), 7.86 (d, J = 15.4 Hz, 1H), 7.68–7.54 (m, 3H), 7.47 (d, J = 15.4 Hz, 1H), 7.08 (dd, J = 8.6, 6.8 Hz, 2H), 5.35 (d, J = 6.1 Hz, 1H), 5.25 (s, 1H), 5.22 (t, J = 4.9 Hz, 3H), 5.15 (t, J = 6.7 Hz, 1H), 5.06 (t, J = 6.8 Hz, 1H), 5.02 (s, 2H), 3.60 (d, J = 2.3 Hz, 3H), 3.50 (d, J = 0.8 Hz, 4H), 3.48–3.36 (m, 4H), 2.23–1.91 (m, 8H), 1.79 (s, 3H), 1.75 (s,3H), 1.66 (m, 6H), 1.58 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 162.3, 160.6, 159.4, 144.4, 144.3, 137.2, 135.6, 131.9, 131.3, 130.3, 128.6, 127.9, 125.4, 124.3, 124.1, 124.0, 123.7, 123.3, 122.6, 122.4, 118.7, 118.6, 116.7, 116.6, 99.9, 94.2, 57.7, 56.2, 39.8, 39.7, 28.2, 27.2, 26.7, 25.7, 23.4, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{39}H_{53}O_6$ $[M+H]^+$ 617.3842; found:617.3852.

*5.1.27. (E)-1-(3-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-(methoxymethoxy)-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (**13d**)*

To a stirred solution of compound **12d** (548.00 mg, 1.00 mmol) in dry toluene (15 mL) was slowly added 100–200 mesh Forisil® (500.00 mg) at room temperature, then the reaction mixture was string at 90 °C for 4 h, After completion of reaction, the reaction mixture was concentrated under vacuum to get a reside which was purified by silica gel column chromatography to afford compound **13d** (90.00 mg, 17%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.27 (s, 1H), 7.86 (d, J = 15.4 Hz, 2H), 7.65–7.53 (m, 3H), 7.47 (d, J = 15.4 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 5.32 (dd, J = 7.7, 6.4 Hz, 1H), 5.26 (d, J = 4.9 Hz, 1H), 5.23 (s, 2H), 5.06 (t, J = 6.8 Hz, 1H), 5.02 (s, 2H), 3.61 (s, 3H), 3.49 (s, 3H), 3.43 (d, J = 6.1 Hz, 2H), 3.38 (d, J = 6.8 Hz, 2H), 2.29–1.88 (4, 1H), 1.79 (m, 3H), 1.75 (s, 3H), 1.64 (s, 3H), 1.57 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 162.2, 160.6, 159.4, 144.3, 135.6, 133.1, 131.3, 130.2, 128.6, 128.1, 125.6, 124.3, 123.8, 122.9, 122.4, 118.7, 116.8, 116.6, 99.9, 94.2, 57.7, 56.2, 39.7, 28.5, 26.7, 25.8, 25.6, 23.4, 18.0, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{34}H_{45}O_6$ $[M+H]^+$ 549.3216; found: 549.3211.

*5.1.28. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-3-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (**2b**)*

To a solution of compound **13b** (60.00 mg, 0.10 mmol) in THF (6 mL), was added 98% H_2SO_4 (0.5 mL), isopropanol (1 ml) at 0 °C, then stirred for 2 h at room temperature, After completion of reaction, the reaction mixture was concentrated under vacuum to get a reside which was purified by silica gel column chromatography to afford compound **2b** (45.00 mg, 79%, purity: 100%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.71 (s, 1H), 7.83 (d, J = 15.4 Hz, 1H), 7.55 (d, J = 8.9 Hz, 3H), 7.46 (d, J = 15.4 Hz, 1H), 6.88 (dd, J = 8.5, 5.2 Hz, 2H), 6.28 (s, 1H), 5.29 (d, J = 5.7 Hz, 3H), 5.11 (dt, J = 23.7, 6.7 Hz, 2H), 3.48 (d, J = 7.1 Hz, 2H), 3.33 (d, J = 7.1 Hz, 2H), 2.12 (m, 8H), 1.83 (s, 3H), 1.81–1.74 (m, 3H), 1.68 (s, 6H), 1.59 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 162.4, 160.3, 157.9, 143.67, 138.9, 138.4, 131.9, 130.5, 128.3, 127.9, 123.9, 121.8, 121.4, 119.0, 118.3, 116.0, 114.3, 113.6, 77.3, 77.0, 76.7, 39.8, 39.8, 32.1, 28.8, 26.9, 26.4, 25.7, 23.5, 21.9, 17.7,16.3. HRMS (ESI) *m/z* Calcd for $C_{35}H_{44}O_4Na$ $[M+Na]^+$ 551.3137; found:. 551.3148.

*5.1.29. (E)-1-(5-((E)-3,7-dimethylocta-2,6-dien-1-yl)-2-hydroxy-4-(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-(methoxymethoxy)phenyl)prop-2en1-one (**2c**)*

The procedure is the same as the preparation of compound **13b** by using compound **12c** (300.00 mg, 0.55 mmol) as substrate to give compound **13c** and no purification to the next step. The procedure is the same as the preparation of compound **2b** by using compound **13c** (60.00 mg, 0.11 mmol) as substrate to give compound **2c** (43.00 mg, 85%, purity: 98%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.68 (d, J = 3.8 Hz, 1H), 7.83 (d, J = 15.4 Hz, 1H), 7.55 (dd, J = 8.5, 5.5 Hz, 3H), 7.45 (d, J = 15.4 Hz, 1H), 6.96–6.78 (m, 2H), 6.23 (d, J = 4.1 Hz, 1H), 5.30 (dd, J = 19.1, 11.9 Hz, 3H), 5.13 (dd, J = 15.6, 7.5 Hz, 1H), 3.46 (d, J = 7.1 Hz, 2H), 3.33 (d, J = 7.1 Hz, 2H), 2.28–2.04 (m, 4H), 1.84 (s, 3H), 1.78 (dd, J = 12.4, 5.2 Hz, 6), 1.68 (s, 3H), 1.60 (s, 6). ^{13}C NMR (100 Hz, $CDCl_3$) δ 192.1, 162.5, 162.4, 160.1, 157.9, 143.7, 138.7, 135.1, 134.9, 132.0, 130.5, 128.5, 128.3, 127.9, 123.8, 122.6, 121.8, 121.5, 121.5, 118.9, 118.7, 118.3, 116.0, 114.6, 113.7, 77.3, 77.0, 76.7, 39.8, 32.1, 29.1, 28.9, 26.8, 26.5, 25.9, 25.8, 25.7, 23.5, 22.0, 18.0, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{30}H_{37}O_4$ $[M+H]^+$ 461.2692; found:. 461.2704.

*5.1.30. Medicagenin (**2a**)*

To a solution of compound **13a** (60.00 mg, 0.10 mmol) in THF (6 mL), was added 98% H_2SO_4 (0.5 mL), isopropanol (1 ml) at 0 °C, then stirred for 2 h at room temperature, After completion of reaction, the reaction mixture was concentrated under vacuum to get a reside which was purified by silica gel column chromatography to afford compound **2a** (40.00 mg, 82%, purity: 97%) as a yellow powder. ^{1}H and ^{13}C NMR identical with literature data [6]; HRMS (ESI) *m/z* Calcd for $C_{25}H_{28}O_4$ $[M+H]^+$ 415.1885; found:. 415.1883.

*5.1.31. (E)-1-(3-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dihydroxy-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (**2d**)*

The procedure is the same as the preparation of Medicagenin **2** by using compound **13d** (60.00 mg, 0.11 mmol) as substrate to give compound **2d** (43.00 mg, 85%, purity: 98%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.71 (s, 1H), 7.83 (d, J = 15.4 Hz, 1H), 7.64–7.51 (m, 3H), 7.46 (d, J = 15.4 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.30 (m, 2H), 5.06 (d, J = 6.6 Hz, 1H), 3.48 (d, J = 7.1 Hz, 2H), 3.32 (d, J = 7.2 Hz, 2H), 2.21–2.02 (m, 4H), 1.83 (s, 3H), 1.79 (m, 6H), 1.68 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 162.4, 160.3,

157.9, 143.7, 139.1, 134.3, 131.9, 130.5, 128.4, 127.9, 123.8, 122.1, 121.3, 119.1, 118.3, 116.0, 114.2, 113.6, 28.9, 26.4, 25.8, 25.7, 21.9, 17.9, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{30}H_{37}O_4$ $[M+H]^+$ 461.2692; found:. 461.2705.

*5.1.32. (E)-1-(2,4-dimethoxy-3,5-bis(3-methylbut-2-en-1-yl) phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**33**)*

To a stirred solution of compound **2a** (100.00 mg, 1.00 mmol) and NaH (41.00 mg, 4.50 mmol) in dry DMF (5 mL) was slowly added CH_3I (126.00 mg, 1.30 mmol) at 0 °C and stirred for 2 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford compound **33** (100.00 mg, 89%, purity: 98%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.67 (d, J = 16 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.31–7.51 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.19–5.29 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.41 (d, J = 6.8 Hz, 2H), 3.31 (d, J = 6.8 Hz, 2H), 1.80 (s, 3H), 1.71–1.73 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 161.6, 159.9, 157.1, 143.6, 132.3, 131.6, 130.8, 130.3, 129.6, 129.3, 129.1, 127.8, 124.1, 123.4, 122.5, 114.4, 77.3, 77.0, 76.7, 63.1, 61.3, 55.4, 28.1, 25.8, 25.7, 23.7, 18.0, 17.9. HRMS (ESI) *m/z* Calcd for $C_{28}H_{34}O_4Na$ $[M+H]^+$ 457.2355; found:. 457.2362.

*5.1.33. (E)-1-(3-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dimethoxy-5-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**34**)*

The procedure is the same as the preparation of compound **33** by using compound **2d** (100.00 mg, 0.22 mmol) as substrate to give compound **34** (92.00 mg, 85%, purity: 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.67 (d, J = 16 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.31–7.51 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.20–5.29 (m, 2H), 5.04–5.08 (m, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.43 (d, J = 6.8 Hz, 2H), 3.35 (d, J = 7.2 Hz, 2H), 1.99–2.10 (m, 4H), 1.80 (s, 3H), 1.73 (m, 6H), 1.64 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 161.6, 160.0, 157.2, 143.6, 132.3, 131.6, 130.8, 130.3, 129.6, 129.3, 129.1, 127.8, 124.1, 123.4, 122.5, 114.4, 77.3, 77.0, 76.7, 63.1, 61.3, 55.4, 39.7, 28.1, 26.6, 25.8, 25.7, 23.6, 17.9, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{33}H_{42}O_4Na$ $[M+H]^+$ 525.2981; found:525.2953.

*5.1.34. (E)-1-(5-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dimethoxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**35**)*

The procedure is the same as the preparation of compound **33** by using compound **2c** (100.00 mg, 0.22 mmol) as substrate to give compound **35** (92.00 mg, 85%, purity: 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.66 (d, J = 16 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.30–7.34 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.06–5.31 (m, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.41 (d, J = 6.4 Hz, 2H), 3.36 (d, J = 6.8 Hz, 2H), 2.02–2.13 (m, 4H), 1.80 (s, 3H), 1.73 (m, 6H), 1.65 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 161.5, 160.0, 157.1, 143.6, 132.3, 131.6, 130.8, 130.3, 129.6, 129.3, 129.1, 127.8, 124.1, 123.4, 122.5, 114.4, 77.3, 77.0, 76.7, 63.1, 61.3, 55.4, 39.7, 28.1, 26.6, 25.8, 25.7, 23.6, 17.9, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{33}H_{42}O_4Na$ $[M+H]^+$ 525.2981; found:525.2984.

*5.1.35. (E)-1-(3-((E)-3,7-dimethylocta-2,6-dien-1-yl)-5-((Z)-3,7-dimethylocta-2,6-dien-1-yl)-2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**36**)*

The procedure is the same as the preparation of compound **33** by using compound **2b** (100.00 mg, 0.22 mmol) as substrate to give compound **36** (92.00 mg, 85%, purity: 95%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.67 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.30–7.35 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.04–5.31 (m, 4H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.43 (d, J = 6.4 Hz, 2H), 3.36 (d, J = 6.8 Hz, 2H), 2.01–2.13 (m, 8H), 1.80 (s, 3H), 1.74 (s, 3H), 1.65–1.73 (m, 6H), 1.57–1.63 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.8, 161.5, 160.0, 157.1, 143.6, 132.3, 131.6, 130.8, 130.3, 129.6, 129.3, 129.1, 127.8, 124.1, 123.4, 122.5, 114.4, 77.3, 77.0, 76.7, 63.1, 61.3, 55.4, 39.7, 27.9, 26.7, 25.8, 25.7, 23.6, 17.7, 16.3. HRMS (ESI) *m/z* Calcd for $C_{38}H_{50}O_4Na$ $[M+Na]^+$ 593.3607; found:593.3607.

5.2. Biology evaluation

5.2.1. Antitumor activity

Human leukemia K562 cells (or human umbilical vein endothelial cells (HUVEC)) were dispensed into a 96 well microplate at 100 μL per well, and incubated for 2 h (or 24 h for HUVEC), and then treated with the compounds at various concentrations (0, 0.01, 0.1, 1, 10, 100 μM). After 48 h of treatment, 20 μL of 5 mg/mL MTT solution was added to each well, and incubated for another 4 h. The cells in each well were then solubilized with DMSO (100 μL for each well) and the optical density (OD) was recorded at 570 nm (or 490 nm for HUVEC). DMSO was used as positive control and the IC_{50} values were derived from the mean OD values of the triplicate tests versus using Graph Pad Prism 5.0.

5.2.2. Flow cytometric analysis of apoptosis

Apoptotic cells were assayed by using the Annexin-V-FITC Apoptosis Detection Kit (BD Biosciences, USA) according to the manufacturer's instruction. In brief, K562 cells were treated with DMSO or chalcone derivatives (30 μM) for 48 h. Cells were then harvested, washed twice with ice-cold PBS and resuspended in 1 × Binding buffer to reach a final concentration of 1×10^6 cells/ml. Cells were stained by adding 5 μL of Annexin-V-FITC and 5 μL of PI (50 μg/mL), sit for 15 min at room temperature in the dark and analyzed by flow cytometry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2015.01.007. These data include MOL files and InChiKeys of the most important compounds described in this article.

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