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Synthesis and screening of novel vitamin E derivatives for anticancer functions

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ABSTRACT

α-TEA, RRR-α-tocopherol ether linked acetic acid, exhibits potent anticancer actions *in vitro* and *in vivo*; whereas, the parent molecule has no anticancer activity. In this study, we incorporated fluorine at the chroman head and/or ether linkage between the chroman head and phytyl tail of α-TEA as well as RRR-α-tocopherol to synthesize 6 vitamin E derivatives, and evaluated the anticancer actions *in vitro* for ability to induce cell death by apoptosis of human MCF-7 and MDA-MB-231 breast cancer cell lines and mouse mammary cancer cell line 66cl-4GFP. All derivatives, with the exception of compound **12**, exhibited anticancer properties. The modified α-TEA ether-type phytyl group exhibited the highest pro-apoptotic activity in comparison with α-TEA as well as other vitamin E derivatives.

1. Introduction

Vitamin E is a general term that describes a family of eight chemically related compounds that are subdivided into two subgroups called tocopherols and tocotrienols, as well as synthetic vitamin E forms [1]. Tocopherols have a basic chemical structure characterized by a long phytyl chain attached at the 2-position of a chromane ring, while tocotrienols differ from that of tocopherols by the presence of three E (*trans*) double bonds in the phytyl tail [2,3]. Moreover, the tocopherols and the tocotrienols have α, β, γ, and δ forms, named on the basis of the number and position of the methyl groups on the chromanol ring. Vitamin E form RRR-α-tocopherol has traditionally been recognized for its free radical-scavenging antioxidant properties that are important for protecting polyunsaturated fats from peroxidation. The antioxidant property of vitamin E is exerted through the phenolic hydroxyl group, which readily donates its hydrogen atom (H) to the lipid peroxyl radical, resulting in the formation of a stable lipid species [4].

Cancer remains a leading cause of deaths worldwide, and despite intense studies the incidence of cancer remains high. Toxicity and resistance to standard drug treatments limit the effectiveness of chemotherapy, highlighting an urgent need for development of potent anticancer drugs with reduced toxicity as new treatment strategies. In recent years, selected tocopherol and tocotrienol forms as well as metabolites [5–7] and synthetic derivatives [8–11] have been reported to have antitumor and anti-inflammatory activities. Of these compounds, the monoester of α-tocopherol, α-tocopheryl succinate, a representative vitamin E analog, has been demonstrated to exhibit anticancer properties in several cancer models and low toxicity to normal cells [12,13]. We developed another vitamin E derivative, α-tocopherol ether-linked acetic acid (α-TEA), that exhibits potent anticancer activity in a wide variety of epithelial cancer cell types, including breast, prostate, lung, colon, ovarian, cervical, and endometrial in cell culture, and significantly reduces tumor burden and metastasis in a syngeneic mouse mammary tumor model, as well as in xenografts of human breast cancer cells [14–21]. Studies also show that α-TEA, in combination with the cyclooxygenase-2 inhibitor celecoxib and the chemotherapeutic drug 9-nitro-camptothecin, significantly decreases tumor burden and metastasis in comparison to single agents [22]. Dietary administration of α-TEA has been shown to significantly reduce tumor volume and lung metastasis in a highly metastatic murine syngeneic model, and to suppress tumor growth and multiplicity of spontaneous murine mammary cancer [20,21].

Chemical modifications of vitamin E, to generate new derivatives can in principle occur at the following distinguishable regions of the molecule (Fig. 1): (I) side chain length and saturation [23–25], (II) the position and geometry (E or Z) of the double bonds [24], (III) heteroatom member of the saturated ring [26–28], (IV)

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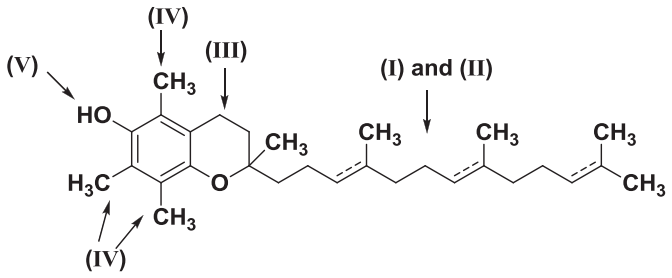


Fig. 1. Modification positions of vitamin E.

numbers of methyl substitutions on the benzene ring [23,29], and (V) esterification and amidation of hydroxyl on the benzene ring [23,24,29–31]. Esterification of hydroxyl on the benzene ring enhances water solubility and potency [32–34]. Amides derived from α- and δ-tocopheramines have been reported to improve anticancer activity [31,32,35].

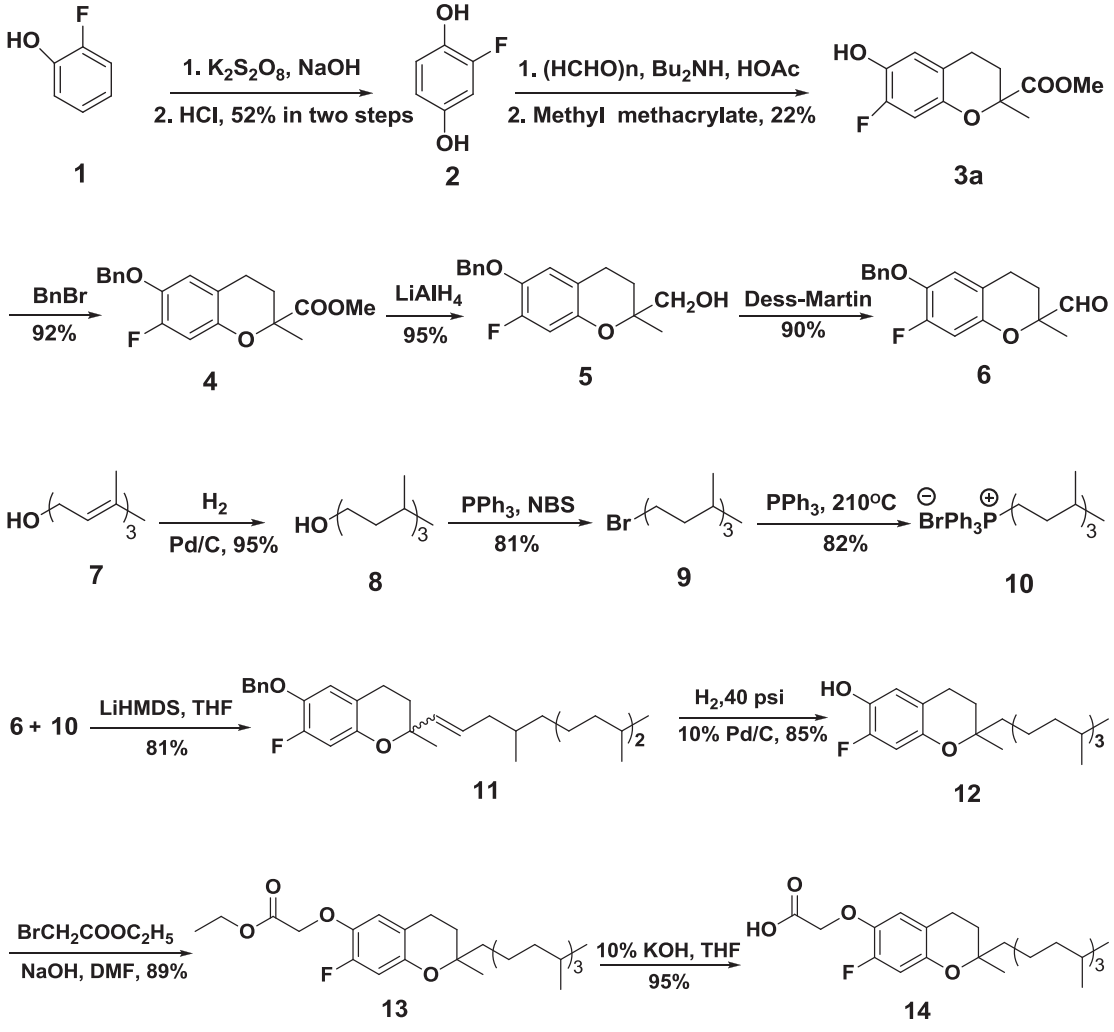
In this study, six novel tocopherol-based derivatives were synthesized and shown to exhibit anticancer properties when tested using human MCF-7 and MDA-MB-231 breast cancer cell lines as well as mouse mammary cancer cell line 66cl-4GFP. Data are presented in two sections for clarity: synthesis of new tocopherol derivatives and testing for anticancer properties.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of fluorinated vitamin E analogs

Fluorine (F) is a small atom with high electronegativity [36] and the carbon–fluorine bond (C–F) is often used in place of strategic carbon–hydrogen bonds (C–H) in drug design strategies, since F is the smallest atom that can replace H [37]. Recent examination of structure–activity relationships during drug discovery and lead compound optimization have shown that fluorinated compounds have advantageous properties in the design of small molecules [36,38]. For example, introduction of fluorine atoms can increase metabolic stability of a compound by blocking the metabolically labile site of the liver enzymes, in particular the P450 cytochromes; replacing H with F can lead to a change in the molecular conformation which may be preferable; and fluorinated compounds can have a significant impact on increasing binding affinity and selectivity of protein–ligand complexes either directly or indirectly by increasing the lipophilicity in pharmaceuticals [36,38]. Since there are limited reports of vitamin E compounds containing fluorine [39], we introduced a fluorine atom on the benzene ring instead of a methyl group to synthesize the title compound **14** in an effort to enhance anticancer properties. The synthetic pathways to generate title compound **14** are depicted in Scheme 1.



Scheme 1. Synthesis routes to compound **14**.

To obtain the fluorinated vitamin E analog **14**, the compound **3** is a key intermediate, which can be generated by the hetero-Diels–Alder reaction of methacrylate with in situ-generated *o*-quinone methides produced from the reaction of para-formaldehyde, dibutylamine and acetic acid [40]. This procedure avoids the use of the high-pressure conditions used to prepare Trolox methyl ester patented by Kazuo [41]. *o*-Fluorophenol **1** was treated with potassium persulfate in sodium hydroxide and then hydrolyzed to give the fluorohydroquinone **2** in 52% yield in two steps via an Elbs oxidation [42,43]. The hetero-Diels–Alder reaction of fluorohydroquinone **2**, methyl methacrylate and para-formaldehyde under reflux conditions in the presence of dibutylamine and acetic acid should have three different products **3a**, **3b** and **3c** (Fig. 2), but we only isolated one product **3a**, where the fluorine atom is located at 6-position on the benzene ring (Fig. 2). The Diels–Alder reaction of *o*-quinone methide and methyl methacrylate provided the ortho regioisomer selectively [44], and the structure of compound **3a** was also confirmed by single crystal X-ray diffraction.

The hydroxyl group at the 6-position on chroman head was protected by benzyl group to give the compound **4** which were reduced by $LiAlH_4$ to obtain the 6-fluorochroman-2-methol, **5**, in 95% yield. The desired intermediate **6** was afforded by Dess–Martin oxidization of **5** in 90% yield. The phytyl side chain was appended via a Wittig coupling with 15-carbon phosphonium bromide **10** [45] in the presence of lithium hexamethyldisilylamide (Li-HMDS) [46–48] to produce the *Z*, *E* mixture **11** in 80% yield. The mixture of alkenes was subjected to catalytic hydrogenation to afford fluorinated vitamin E derivative **12** in 85% yield. The target fluorinated tocopherol ether-linked acetic acid **14** was synthesized according to the reported method [49] with minor modifications.

2.1.2. Synthesis of ether-type phytyl group-modified vitamin E derivatives

In our group, we found α-TEA is a potent inducer of apoptosis in a wide variety of epithelial cancer cell types, in an effort to enhance the anticancer properties of RRR-α-tocopherol derivative and find a better lead tocopherol derivative, we introduced an oxygen atom in the side chain of α-TEA to obtain compounds **22a** and **22b** (Scheme 2). This change may improve the molecule's hydrophilicity which affect bioavailability, and then enhance anticancer activities.

Trolox methyl ester **16a** and **16b** are readily prepared from the commercial free acid via methyl esterification. The intermediates **18** were obtained according to the identical procedure. In order to generate the ether side chain molecule **22** series, **18a**,**b** were treated with bromo-3,7,11-trimethyldodecane **9** in the presence of NaH in THF under reflux to afford the corresponding **19a**,**b** in 62–76% yield, which were subjected to hydrogen over palladium catalyst to give the de-protected hydroxyl group **20a**,**b**, and then followed the above procedure to afford the target compounds **22a**,**b** in good yields.

2.1.3. Synthesis of ether-type phytyl group-modified fluorinated vitamin E derivatives

After obtaining the ether-type phytyl group-modified α-TEA, it is easy to get the fluorinated ethyl-type phytyl α-TEA derivatives. Compound **5** was alkylated with compound **9** (Scheme 1) in the presence of NaH and THF under reflux to afford the compound **23** in 62% yield. The target compound **26** was obtained by the identical procedure to the synthesis of compounds **22** in good yields (Scheme 3).

In the above reactions, the phytyl group or ether-type phytyl group was obtained from the mixture isomers of farnesol, which was reduced and brominated to the *all-rac*-bromotrimethyldodecane, so the final compounds have two or three chiral carbon centers, and

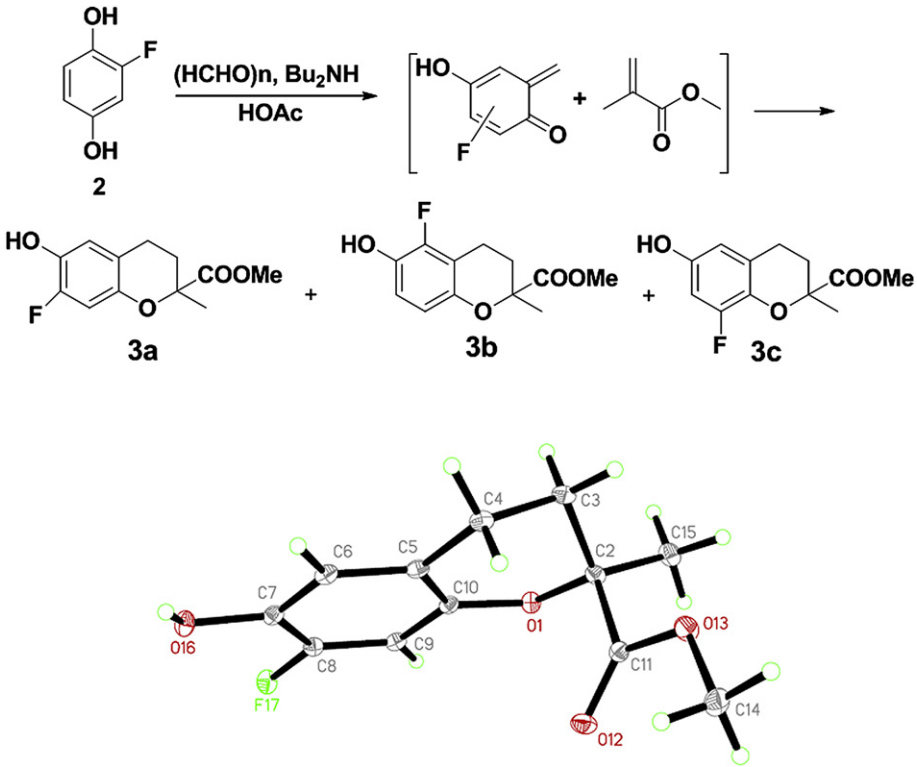
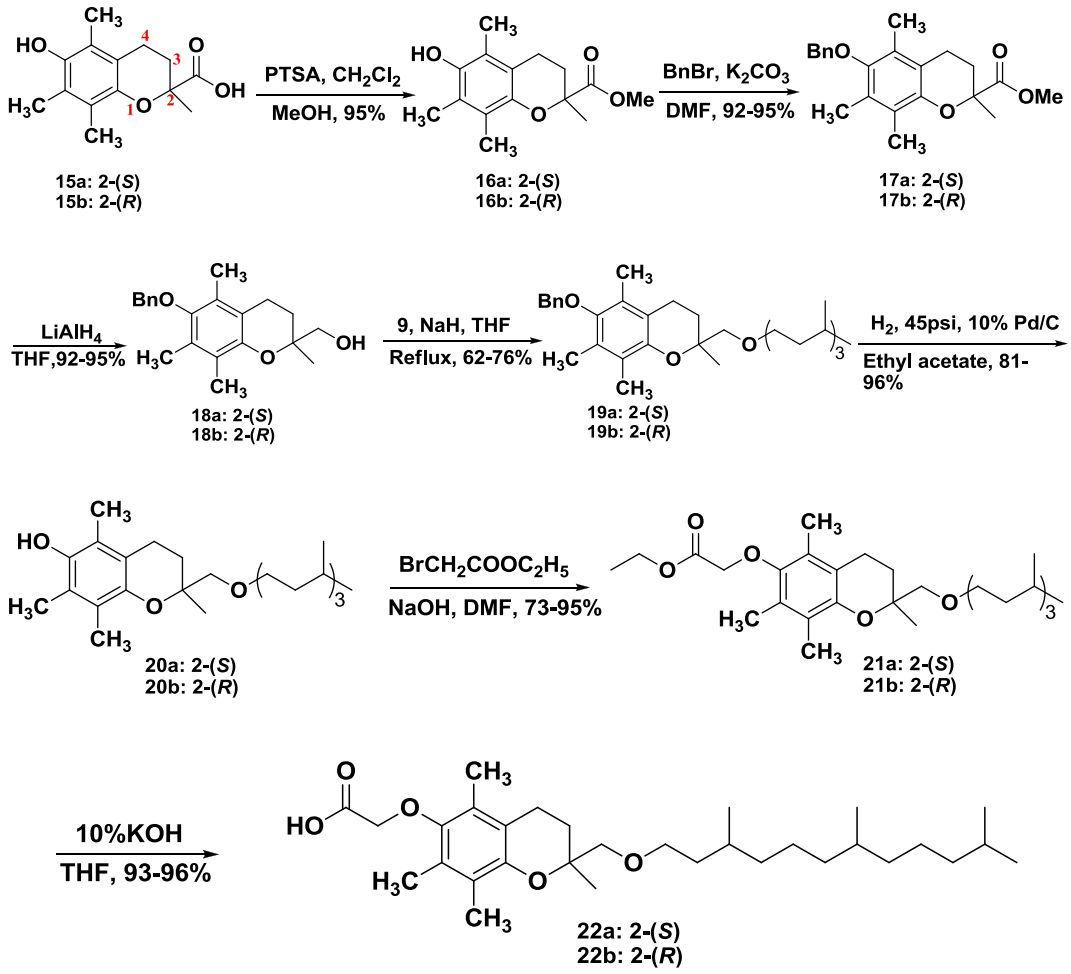


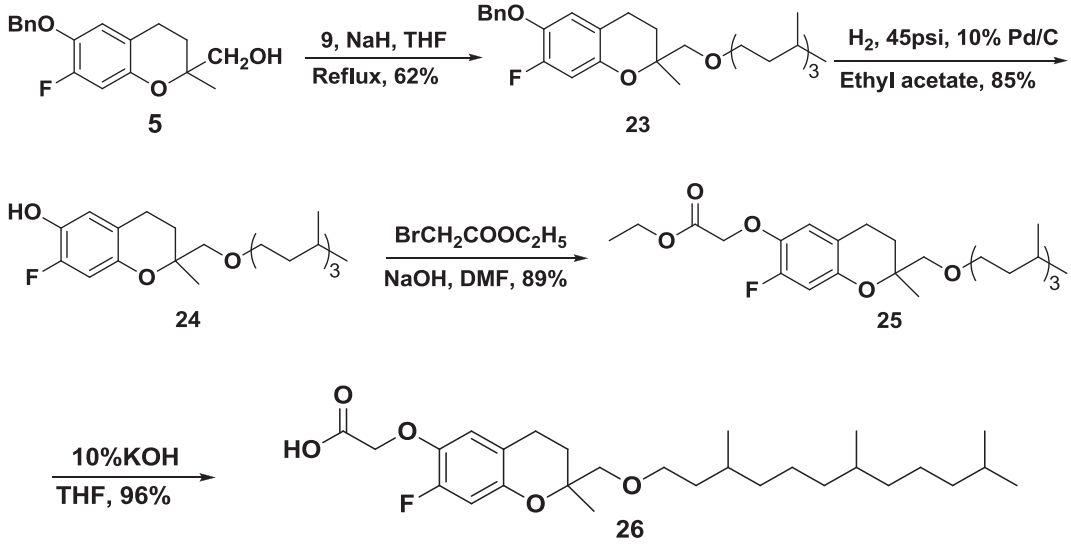
Fig. 2. The intermediate **3** generation procedure and its crystal structure.



Scheme 2. Synthesis routes to compounds **22a** and **22b**.

there is a racemic mixture (*all-rac*) of four or eight stereoisomers, which was confirmed by ^{13}C NMR spectrum, and the side chain carbons (2-CH_3, 2′, 3′, 4′, 4′-CH_3, 5′, 8′, and 9′) in all-racemic mixture of eight stereoisomers give more than one resonance signal [50].

In summary, the compounds prepared in this work can be divided into three groups (Fig. 3): (i) fluorinated RRR-α-tocopherol (compound **12**) and α-TEA (compound **14**) derivative, (ii) ether-type phytyl group modified α-TEA (compound **22a** and **22b**), and (iii)



Scheme 3. Synthesis routes to compound **26**.

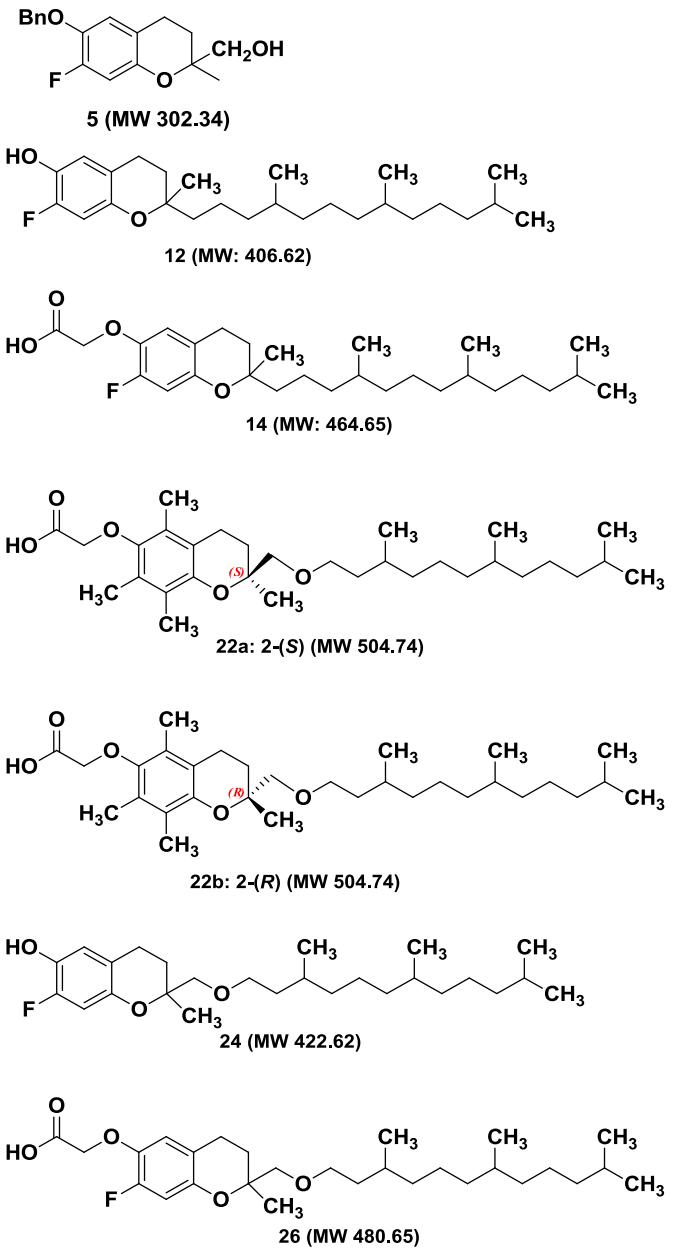


Fig. 3. Structures and molecular weights of novel fluorinated and ether linked phytyl tail vitamin E compounds (Compound **5** as a control).

ether-type phytyl group modified fluorinated RRR-α-tocopherol (compound **24**) and α-TEA (compound **26**).

2.2. Screening of novel vitamin E derivatives for pro-apoptotic properties

The pro-apoptotic properties of prepared vitamin E derivatives depicted in Fig. 4 were evaluated by Western blot analyses for polyADP-ribose polymerase (PARP) cleavage, a caspase-dependent apoptotic marker, following treatments of murine mammary (66cl-4GFP) cells and human breast cancer MCF-7 and MDA-MB-231 cells. As shown in Fig. 4A, novel vitamin E derivatives **22a**, **22b** and **26** exhibited markedly increased PARP cleavage in comparison with α-TEA in all three cell lines, suggesting that these derivatives possess superior pro-apoptotic activity in comparison to α-TEA. Compound **14** also exhibited increased PARP cleavage in 66cl-4GFP and MCF-7 breast cancer cells in comparison with α-TEA (Fig. 4A). **24** exhibited increased PARP cleavage only in MCF-7 cells in comparison with α-TEA (Fig. 4A). Compound **12** did not induce apoptosis as verified by inability to cleave PARP (Fig. 4A).

To further confirm the pro-apoptotic activity of the analogs that exhibited increased PARP cleavage in comparison with α-TEA, we conducted Annexin V/PI/FACS assay to quantify apoptotic induction in MCF-7 and MDA-MB-231 human breast cancer cell lines. Data show that compound **22a**, **22b** and **26** at 20 μM and 40 μM significantly induced increased levels of apoptosis in MDA-MB-231 cells (Fig. 4B) and, MCF-7 cells at 20 and 40 μM for **22a** and 40 μM for **22b** and **26** (Fig. 4C), respectively, in comparison with α-TEA. EC-50 values of apoptosis as determined by Annexin V assay, for α-TEA, **14**, **22a**, **22b** and **26** were 35, 34, 18, 16 and 27 μM in MDA-MB-231 cells and 51, 60, 21, 29 and 35 μM in MCF-7 cells, respectively (Table 1). Based on structure modifications, data demonstrated that; (i) fluorinated RRR-α-tocopherol (compound **12**) did not exhibit pro-apoptotic activity (no PARP cleavage) and ether-type phytyl group-modified fluorinated RRR-α-tocopherol (compound **24**) induced PARP cleavage only in MCF-7 cells, (ii) fluorinated α-TEA (compound **14**) showed enhanced PARP cleavage, but did not show enhanced apoptosis detected by Annexin V in MCF-7 cells in comparison to α-TEA. Compound **14** did not show increased apoptosis in comparison with α-TEA by either PARP cleavage or Annexin V assay in MDA-MB-231 cells, leading to the conclusion that compound **14** is not a potential candidate as an effective novel anticancer compound, (iii) ether-type phytyl group-modified α-TEA (S and R forms) (**22a** and **22b**) significantly enhanced apoptosis tested by both PARP cleavage and Annexin V, and are the best vitamin E analogs based on pro-apoptotic activity among the tested derivatives, also the apoptosis isn't affected by the configuration of the 2-position and (v) based on EC-50 apoptotic values (Table 1), ether-type phytyl group-modified fluorinated α-TEA (compound **26**) exhibit less pro-apoptotic property than fluorinated α-TEA, suggesting that the inclusion of fluorine in the ether-type phytyl group modified α-TEA in such a way as to reduce the pro-apoptotic activity.

α-TEA (RRR-α-tocopherol ether linked acetic acid), a RRR-α-tocopherol analog, derived from RRR-α-tocopherol exhibits anticancer properties *in vitro* and *in vivo*; while, parent compound RRR-α-tocopherol does not. Goal of these studies was to develop new and more effective vitamin E derivatives, in comparison to α-TEA, for anticancer therapeutics. To achieve this goal, we incorporated fluorine at the chroman head and/or ether linkage between chroman head and phytyl tail of α-TEA and RRR-α-tocopherol, and tested these derivatives for their pro-apoptotic action *in vitro* using human breast cancer cells as well as a mouse mammary cancer cell line. Data presented here demonstrated that ether-type phytyl group modified α-TEA exhibited the most potent pro-apoptotic property in comparison to other vitamin E derivatives and α-TEA. Data show that ether-type phytyl group modified α-TEA is a novel vitamin E derivative with potent anticancer activity that merits further investigation.

Modification of a compound to enhance its biological functions can be achieved via different ways (mechanisms) including improving its bioavailability (uptake and stability) and binding activity as well as reaching new targets. Our *in vitro* data show that addition of an ether linkage between the chroman head and phytyl tail (Compound **22a** and **22b**) of α-TEA can improve the pro-apoptotic property of α-TEA. However, the mechanism (s) whereby ether-type phytyl group modified α-TEA enhances pro-apoptotic activity in comparison with α-TEA is not known. Although this modification has been reported to reduce the anti-oxidant activity of vitamin E compounds [25], it may not apply for the increased anticancer activity, because α-TEA has no antioxidant

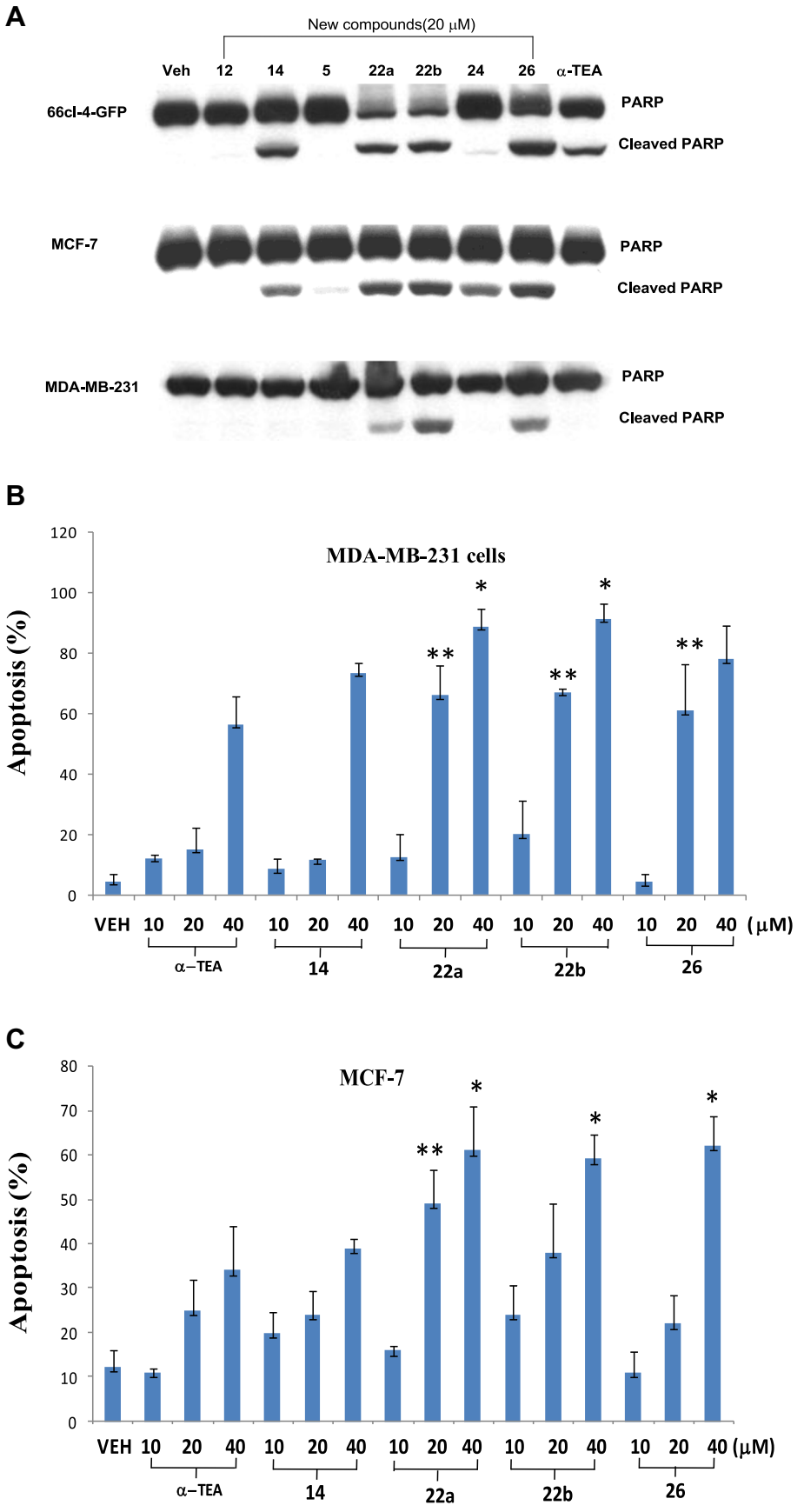


Fig. 4. Evaluating the ability of novel vitamin E analogs to induce apoptosis. (A) Western blot analyses were used to evaluate efficacy of different compounds to cleave PARP on MDA-MB-231, MCF-7 and 66cl-4GFP cells. Cells were treated with different compounds at 20 μM or vehicle control (VEH) for 15 h. Data are representative of two separate

Table 1
EC-50 values of apoptosis (μM).[a]

Cancer cell line	Compound				
	α-TEA	**14**	**22a**	**22b**	**26**
MDA-MB-231	35	34	18	16	27
MCF-7	51	60	21	29	35

[a] The cells were treated with different concentrations of vitamin E analogs followed by Annexin V assay to determine apoptosis. EC-50 values were determined using commercially available software (Calcusyn; Biosoft, Manchester, UK).

activity. Based on the modified structure, addition of an ether linkage between the chroman head and phytyl tail may further increase the hydrophilicity of the total molecule, leading to more uptake. It is also possible that the polar change alternates the structure of the modified α-TEA, leading to increased binding activity to its target or triggering a new target. Further study will be definitely needed to address these questions.

The number of chroman head methyl group exhibits inverse correlation with anticancer efficacy [17], reduction in number of methyl groups will increase anticancer efficacy. So we hypothesized that decrease of the electron density on the chroman head will improve the anticancer properties of α-TEA derivatives by reduction of methyl group and addition of a fluorine in vitamin E compounds. Fluorine is a small molecule and has been reported to increase the bioavailability when cooperated into some pharmaceutical compounds [51]. In this regard, we developed fluorinated vitamin E compounds such as fluorinated RRR-α-tocopherol (compound **12**), fluorinated α-TEA (compound **14**) and fluorinated α-TEA with an ether linkage between the chroman head and phytyl tail (Compound **26**) derivatives. To our surprising, we did not see the better anticancer activity of these fluorinated vitamin E compounds in comparison with their parental compounds by testing *in vitro* pro-apoptotic property. These data suggest that cooperation of fluorine may increase the bio-functions in some compounds, but not all. Why cooperation of fluorine into vitamin E compound cannot improve their *in vitro* anticancer activity is still unknown. Since the difference in bioavailability of vitamin E between *in vitro* and *in vivo*, further *in vivo* anticancer test is needed to confirm if fluorinated vitamin E compounds possess better anticancer property.

3. Conclusions

In this study we synthesized 6 novel vitamin E derivatives by incorporating fluorine at the chroman head and/or ether linkage between the chroman head and phytyl tail of α-TEA as well as RRR-α-tocopherol and tested their *in vitro* anticancer property on human breast cancer and mouse mammary cancer cell lines. Data suggest that ether-type phytyl group modified α-TEA (**22a** and **22b**) possess better anticancer potential than α-TEA and merit further *in vivo* evaluation and mechanistic study.

4. Experimental section

4.1. Chemistry

Dichloromethane was distilled from CaH_2. THF was distilled from Na/benzophenone. All other chemicals were purchased from Sigma–Aldrich, Fluka, and Acros and used without further purification.

All water-sensitive syntheses were performed under an inert atmosphere of argon using standard Schlenk techniques. ^1H and ^{13}C NMR data were collected on Varian Mercury 300 MHz and 600 MHz spectrometers at 300 MHz, 600 MHz and 75 MHz, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm and are referenced downfield from $(CH_3)_4Si$ using the residual solvent peak as an internal standard. High resolution mass spectra (HRMS) were obtained with a VG analytical ZAB2-E instrument (ESI). Melting point was measured on the Buchi Melting Point B-540, and the temperature was not corrected. TLC analyses were performed on glass sheets pre-coated with silica gel (Silica Gel 60, F254, 0.25 mm Layer Thickness). Column chromatographic separations were carried out on silica gel (Silica Gel 60, 200 × 400 mesh) under pressure.

4.1.1. Preparation of 2-fluoro-1,4-hydroquinone **2**

To the 2-fluorophenol **1** (5.6 g, 50.0 mmol) dissolved in 6% aqueous NaOH (200 mL), was added solid potassium persulfate (13.5 g, 50.0 mmol) with stirring in several portions over 10 min to result in a dark solution. This dark solution was stirred overnight at room temperature, then concentrated to *ca*. one third of its original volume under reduced pressure. The solution was cooled to 0 °C, neutralized to pH 6.5 with concentrated HCl and extracted once with diethyl ether (100 mL). This organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to reisolate the unreacted starting material, 2-fluorophenol, using flash silica gel column chromatography with hexane/ethyl acetate (V/V 6:1) as eluent to give 2.0 g 2-fluorophenol.

The aqueous solution was acidified with concentrated HCl (50 mL), refluxed for 1 h, then concentrated to *ca*. 50 mL under reduced pressure. Addition of acetone (100 mL) precipitated the inorganic salts, which were removed by filtration. The filtrate was taken to dryness on the rotary evaporator and the dark residue, dissolved in acetone, was coated on silica gel (10 g). The dry material was subjected to column chromatography (hexane/ethyl acetate 3:1) to give the product 2.2 g, white solid, m.p. 120–121 °C, yield 52%, R_f 0.30 (20% EtOAc in hexane).

^1H NMR (300 M, $CDCl_3$): 6.51–6.56 (m, 1H), 6.64–6.69 (m, 1H), 6.85–6.92 (m, 1H), 4.77 (brs, 2H, 2× OH).

EI-MS Calcd. for $C_6H_5FO_2$ 128 (M^+), found 129 $(M+1)^+$, 128 (M^+).

4.1.2. Preparation of methyl 7-fluoro-6-hydroxychroman-2-carboxylate **3**

To the mixture of paraformaldehyde (0.23 g, 6.87 mmol, 1.2 eq), methyl methacrylate (3.2 g, 3.4 mL, 31.25 mmol, 5.0 eq), and acetic acid (3.5 mL), was added 2-fluoro-1, 4-hydroquinone **2** (0.8 g, 6.25 mmol, 1.0 eq), then dibutylamine (0.096 g, 0.127 mL, 0.75 mmol, 0.12 eq) was added. After the mixture was heated to 120 °C for 24 h, the excess acetic acid was evaporated and diluted with ethyl acetate (50 mL), washed with saturated $NaHCO_3$, NH_4Cl and water, successively, dried over Na_2SO_4. Most of solvent was evaporated and silica gel (5.0 g) was added, then the total solvent was evaporated and the residue was separated by flash silica gel column chromatography using hexane/ethyl acetate (3:1 to 2:1) as eluent to give the title compound 0.31 g, colorless oil, stand at room temperature overnight to give the white solid, m.p. 78–79 °C, yield 21%, R_f 0.36 (20% EtOAc in hexane).

^1H NMR (δ/ppm, 300 M, $CDCl_3$): 1.61 (s, 3H, CH_3), 1.82–1.92 (m, 1H, 3-CH_2), 2.34–2.43 (m, 1H, 3-CH_2), 2.61–2.67 (m, 2H, 4-CH_2), 3.73 (s, 3H, $COOCH_3$), 4.90 (brs, 1H, OH), 6.64–6.71 (dd, 2H, J = 11.27, 8.36 Hz).

experiments. (B and C) MDA-MB-231 and MCF-7 cells were treated with different concentrations of tested compounds or VEH for 15 h. Apoptosis was determined by FACS/Annexin V analyses. Data are presented as the mean + SD of three independent experiments. *Significantly different from α-TEA at 40 μM ($P < 0.05$) and **significantly different from α-TEA at 20 μM.

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 22.31, 25.37, 30.55, 52.88, 78.29, 104.41, 104.69, 116.75, 116.79, 116.96, 116.99, 137.44, 137.63, 147.00, 147.14, 148.54, 151.67, 174.29.

HREI-MS Calcd. for $C_{12}H_{14}FO_4$ (M + 1) 241.0876, found 241.0871.

To determine the exact position of fluorine atom at the chroman ring, we grew the single crystal of compound **3**, and found the fluorine atom is located at the 7-position of chroman head.

4.1.3. Preparation of methyl 7-fluoro-6-benzylchroman-2-carboxylate **4**

To the mixture of 7-fluoro-6-hydroxychroman-2-carboxylate **3** (0.17 g, 0.71 mmol) in 5 mL of DMF, was added K_2CO_3 (0.147 g, 1.06 mmol, 1.5 eq) under ice-bath. After the mixture was stirred for 20 min, benzyl bromide (0.146 g, 0.85 mmol, 1.2 eq) was added and the mixture was stirred at room temperature overnight. The reactant was diluted with 10 mL of water and 15 mL of ethyl acetate, the aqueous was extracted with ethyl acetate (15 mL × 2), the combined ethyl acetate phase were washed with water (20 mL × 2), dried over Na_2SO_4. The solvent was evaporated and the residue was separated by silica gel column chromatography using eluent (10% ethyl acetate in hexane) to give white solid, m.p. 125–126 °C, 0.21 g, yield 92%, R_f 0.34 (10% EtOAc in hexane).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.62 (s, 3H, CH_3), 1.82–1.92 (m, 1H, 3-CH_2), 2.36–2.44 (dt, 1H, J = 4.5, 13.5 Hz, 1H, 3-CH_2), 2.60–2.64 (dd, 2H, J = 4.5, 8.4 Hz, 4-CH_2), 3.73 (s, 3H, $COOCH_3$), 5.04 (s, 2H, CH_2Ph), 6.65–6.73 (dd, 2H, J = 12.1, 9.1 Hz).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 22.45, 25.41, 30.54, 52.82, 72.75, 78.32, 105.39, 105.67, 115.87, 115.92, 117.11, 117.14, 127.77, 128.23, 128.76, 137.20, 140.82, 140.97, 148.08, 148.22, 150.81, 154.05, 174.03.

EI-MS for $C_{19}H_{19}FO_4$ Calcd. 330.4 (M^+), found 330, 271, 253, 279, 171.

4.1.4. Preparation of (6-benzyloxy-7-fluoro-2-methyl-chroman-2-yl)methanol **5**

In 100 mL of flask, was placed $LiAlH_4$ (0.17 g, 4.5 mmol) in 10 mL of dry THF, then methyl 7-fluoro-6-benzylchroman-2-carboxylate **4** (0.30 g, 0.9 mmol) in 10 mL of dry THF was added dropwise under 0 °C with stirring. After addition, the mixture was stirred at 0 °C for 1 h, then warmed to room temperature for 2 h. After the TLC show there is no starting material, the reactant was quenched with saturated NH_4Cl aqueous under ice-bath, filtered and concentrated, then diluted with 40 mL of ethyl acetate, washed with brine (20 mL × 2), water (20 mL × 1), successively, dried over Na_2SO_4. The solvent was evaporated and the residue was separated by silica gel column chromatography using hexane and ethyl acetate (V/V 4:1) as eluent to give an oil, 0.27 g, yield 95%, stood at room temperature for overnight to become a white solid, m.p. 74–75 °C, R_f 0.31 (20% EtOAc in hexane).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.25 (s, 3H, CH_3), 1.65–1.73 (m, 1H, 3-CH_2), 1.95–2.05 (m, 1H, 3-CH_2), 2.62–2.82 (m, 2H, 4-CH_2), 3.56–3.66 (q, 2H, J = 11.48 Hz, $\underline{CH_2}OH$), 5.06 (s, 2H, CH_2Ph), 6.58–6.74 (dd, 2H, J = 12.1, 9.2 Hz), 7.34–7.47 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 20.74, 21.67, 27.72, 69.20, 72.89, 76.90, 105.58, 105.86, 116.32, 116.36, 117.47, 117.51, 127.82, 128.25, 128.78, 137.24, 140.42, 140.57, 147.99, 148.12, 150.82, 154.06.

EI-MS Calcd. for $C_{18}H_{19}FO_3$ 302 (M^+), found 302, 285, 231, 225, 211, 195, 141.

4.1.5. Preparation of 6-benzyloxy-7-fluoro-2-methyl-chroman-2-carbaldehyde **6**

To the mixture of (6-benzyloxy-7-fluoro-2-methyl-chroman-2-yl)methanol **5** (0.17 g, 0.56 mmol) in 20 mL of dry CH_2CH_2, was added Dess–Martin periodinane (15 wt.%, 2.5 mL) at room temperature. After addition, the mixture was stirred for 1 h at room temperature. After the starting material was disappeared, the reactant was concentrated and the residue was separated by silica gel column chromatography (hexane/ethyl acetate V/V 5:1) to give the title aldehyde compound, oil, stand to be white solid, m.p. 89–90 °C, 0.15 g, yield 90%. R_f 0.15 (hexane/ethyl acetate V/V 25:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.41 (s, 3H, CH_3), 1.77–1.87 (m, 1H, 3-CH_2), 2.19–2.77 (dt, 1H, J = 5.54 Hz, 13.67 Hz, 3-CH2), 2.62–2.66 (m, 2H, 4-CH_2), 5.06 (s, 2H, CH_2Ph), 6.67–6.76 (dd, 2H, J = 11.9, 9.0 Hz), 7.34–7.46 (m, 5H, C_6H_5).

HR-EIMS Calcd. for $C_{18}H_{17}FO_3$ 300.1162 (M^+), found 300.1163.

4.1.6. 3,7,11-Trimethyldodecanol **8**

A mixture of farnesol **7** (20.0 g, 89.94 mmol) and 10% Pd/C (3.0 g) in ethyl acetate (100 mL) was hydrogenated under 40 PSI for 5.5 h. The catalyst was removed by filtering on a short pad of celite, the filtrate was evaporated and the residue was purified by flash column chromatography on silica gel to give 19.0 g, yield 95%, colorless liquid, R_f 0.6 (20 %EtOAc in hexane), ^{1}H NMR (δ/ppm, 300 MHz, $CDCl_3$) 3.66 (m, 2H), 1.49–1.59 (m, 4H), 1.01–1.40 (m, 14H), 0.81–0.88 (m, 12H).

4.1.7. 1-Bromo-3,7,11-trimethyldodecane **9**

To a solution of 3,7,11-trimethyldodecanol **8** (4.56 g, 0.02 mmol) in CH_2Cl_2 (10 mL), was added triphenyl phosphine (5.8 g, 0.022 mmol). The clear solution was cooled in ice batch and N-bromosuccinimide was added in portions, keeping the temperature less than 30 °C. The mixture was subsequently stirred for 1 h at 25 °C, evaporated in vacuo, and treated with hexane (20 mL × 3), filtered and concentrated to give crude product. It was purified by flash column chromatography on silica gel to give colorless liquid 4.67 g, yield 81%,, R_f 0.9 (100% hexane).

^{1}H NMR (δ/ppm, 300 MHz, $CDCl_3$) 3.37–3.52 (m, 2H), 1.83–1.96 (m, 1H), 1.47–1.74 (m, 3H), 1.03–1.44 (m, 13H), 0.85–0.91 (dd, 12H, J = 6.48 Hz).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 40.35, 40.27, 39.59, 37.59, 37.51, 37.49, 37.46, 37.07, 37.01, 33.00, 32.97, 32.48, 31.92, 31.88, 28.22, 25.05, 25.03, 24.46, 22.96, 22.86, 19.97, 19.90, 19.24, 19.17.

EI-MS Calcd. for $C_{15}H_{31}Br$ 291 (M^+), found 291, 289, 249, 207, 177, 141, 127.

4.1.8. Triphenyl (3,7,11-trimethyldodecyl)phosphonium bromide **10**

The mixture of triphenyl phosphine (2.88 g, 11.0 mmol) and 1-bromo-3,7,11-trimethyldodecane **9** (2.9 g, 10 mmol) was heated to 210 °C under Argon for 6 h, then cooled to room temperature and diluted with ethyl ether (30 mL), centrifuged, and repeated the step for 3 times until no triphenyl phosphine, dried under vacuum to give 1.8 g viscous solid, yield 82%.

^{1}H NMR (δ/ppm, 300 MHz, $CDCl_3$) 3.71–3.84 (m, 2H), 2.33–2.42 (m, 2H), 1.75–1.87 (m, 1H), 1.45–1.57 (m, 2H), 1.05–1.35 (m, 12H), 0.80–1.01 (ddd, 12H, J = 6.43, 6.59, 6.32 Hz).

4.1.9. Preparation of 6-benzyloxy-7-fluoro-2-methyl-2-(4′,8′,12′-trimethyl-tridecenyl)-2, 3-dihydro-benzofuran (**11**)

To the mixture of triphenyl (3,7,11-trimethyldodecyl)phosphonium bromide **10** (0.6 g, 1.32 mmol) in dry THF (10 mL), was added LiHMDS (1 M in THF, 2 mL, 2.0 mmol) under −78 °C. After addition, the mixture was stirred for 30 min and then 6-benzyloxy-7-fluoro-2-methyl-chroman-2-carbaldehyde **6** (0.6 g, 1.32 mmol) in dry THF (10 mL) was added under −78 °C. After the mixture was stirred for 30 min at −78 °C and another 30 min at 0 °C, then refluxed for 1.5 h, then solvent was evaporated and diluted with saturated NH_4Cl, extracted with CH_2Cl_2 (20 mL × 3), the combined extracts were dried over $MgSO_4$, and separated by silica gel column chromatography (100% hexane to 4% ethyl acetate in hexane) to obtain the colorless oil, 0.32 g, yield 81%.

^{1}H NMR (δ/ppm, 600 M, $CDCl_3$): 0.77–0.87 (m, 12H, 4× CH_3), 1.03–1.09 (m, 3H), 1.11–1.15 (m, 2H), 1.20–1.31 (m, 7H), 1.34–1.39 (m, 2H), 1.46 (d, J = 1.96 Hz, 3H, 2-CH_3), 1.49–1.54 (m, 1H), 1.71–1.75 (m, 1H), 1.91–2.04 (m, 1H), 2.11–2.23 (m, 1H), 2.27–2.40 (m, 1H), 2.55–2.59 (dt, J = 4.9, 16.3 Hz, 1H), 2.68–2.73 (m, 1H), 5.02 (s, 2H, CH_2Ph), 5.31–5.38 (m, 2H, CH=CH), 6.55–6.67 (dd, 2H, J = 9.22, 12.27 Hz, 5, 8-phenyl H), 7.28–7.43 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 125 M, $CDCl_3$): 19.57, 19.58, 19.63, 19.64, 19.67, 19.70, 19.74, 19.77, 22.34, 22.65, 22.74, 24.55, 24.56, 24.63, 24.82, 24.83, 24.84, 27.39, 27.42, 28.00, 32.78, 32.80, 32.81, 32.82, 33.04, 33.07, 33.58, 33.60, 33.61, 35.09, 35.18, 35.30, 37.05, 37.10, 37.28, 37.31, 37.32, 37.35, 37.39, 37.41, 37.42, 37.43, 39.39, 72.71, 72.74, 77.10, 77.13, 105.28, 105.29, 105.42, 105.43, 116.59, 116.61, 116.64, 117.20, 117.22, 117.25, 117.27, 127.55, 127.57, 127.93, 127.94, 128.49, 132.01, 132.03, 132.06, 132.08, 132.87, 132.90, 137.16, 137.17, 140.02, 142.05, 142.10, 142.13, 148.35, 148.42, 151.32, 151.33, 152.94, 152.95.

HR-EIMS Calcd. for $C_{33}H_{47}FO_2$ 494.3560 (M^+), found 494.3565.

4.1.10. Preparation of 6-hydroxy-7-fluoro-2-methyl-2-(4′,8′,12′-trimethyl-tridecenyl)-2,3-dihydro-benzofuran (**12**)

The mixture of 6-benzyloxy-7-fluoro-2-methyl-2-(4′,8′,12′-trimethyltridecenyl)-2,3-dihydro-benzofuran **11** (0.4 g, 0.8 mmol) and 10% Pd/C (0.1 g) in ethyl acetate (20 mL) was hydrogenated under 45 PSI hydrogen atmosphere for 24 h. The mixture was filtered, and concentrated, the residue was separated by silica gel column chromatography (hexane/ethyl acetate V/V 10:1) to give the oil, 0.28 g, yield 85%, R_f 0.3 (hexane/ethyl acetate V/V 10:1).

^{1}H NMR (δ/ppm, 600 M, $CDCl_3$): 0.84–0.87 (m, 12H, 4× CH_3), 1.03–1.15 (m, 6H), 1.20–1.42 (m, 14H), 1.48–1.59 (m, 4H), 1.69–1.81 (m, 2H), 2.65–2.67 (m, 2H, 4-CH_2), 4.59 (brs, 1H, OH), 6.51–6.67 (dd, 2H, J = 9.80, 11.82 Hz, 5, 8-phenyl H).

^{13}C NMR (δ/ppm, 125 M, $CDCl_3$): 19.57, 19.58, 19.63, 19.64, 19.65, 19.71, 20.97, 20.98, 20.99, 21.00, 22.58, 22.68, 23.94, 23.95, 24.41, 24.42, 24.76, 24.77, 27.95, 30.78, 30.81, 32.64, 32.66, 32.73, 32.74, 32.75, 37.30, 37.31, 37.35, 37.40, 37.42, 37.43, 39.73, 39.78, 60.36, 76.16, 104.28, 104.41, 116.58, 116.60, 117.07, 117.09, 136.27, 136.37, 147.35, 147.41, 148.95, 150.52.

HR-EIMS Calcd. for $C_{26}H_{43}FO_2$ 406.3247 (M^+), found 406.3253.

4.1.11. Preparation of ethyl 2-(7-fluoro-2-methyl-2-(4′,8′,12′-trimethyl-tridecyl)-chroman-6-yloxy) acetate (**13**)

To the mixture of 6-hydroxy-7-fluoro-2-methyl-2-(4′,8′,12′-trimethyltridecenyl)-2,3-dihydro-benzofuran **12** (0.1 g, 0.25 mmol) in DMF (5 mL), was added ethyl bromoacetate (50 mg, 0.3 mmol), and then powder NaOH (15 mg, 0.375 mmol) was added, the mixture was stirred at room temperature until there is no starting material and diluted with ethyl acetate (20 mL) and brine (10 mL), the aqueous was extracted with ethyl acetate (10 mL × 2), the combined ethyl acetate were washed with brine (10 mL × 2), water (10 mL × 1), dried over $MgSO_4$. After removal of the solvent, the residue was separated by silica gel column chromatography (10% ethyl acetate in hexane) to give the colorless oil, 0.26 g, yield 89%.

^{1}H NMR (δ/ppm, 600 M, $CDCl_3$): 0.81–0.85 (m, 12H, 4× CH_3), 1.00–1.05 (m, 6H), 1.18–1.40 (m, 18H), 1.46–1.56 (m, 3H), 1.67–1.72 (m, 1H), 1.75–1.80 (m, 1H), 2.59–2.67 (m, 2H), 4.22–4.25 (q, 2H, J = 7.14 Hz), 4.59 (s, 2H, O$\underline{CH_2}$Ph), 6.51 (d, 1H, J = 12.45 Hz), 6.68 (d, 1H, J = 9.24 Hz).

^{13}C NMR (δ/ppm, 125 M, $CDCl_3$): 169.13, 153.04, 151.42, 149.42, 149.35, 139.01, 138.93, 118.31, 118.30, 116.31, 116.29, 105.58, 105.44, 76.42, 68.37, 68.36, 61.19, 39.90, 39.87, 39.36, 37.53, 37.52, 37.45, 37.44, 37.42, 37.39, 37.38, 37.379, 37.374, 37.34, 37.33, 37.27, 32.77, 32.75, 32.70, 32.68, 30.71, 30.69, 27.96, 24.79, 24.78, 24.44, 23.99, 23.98, 22.70, 22.61, 21.81, 21.00, 20.99, 19.73, 19.66, 19.65, 19.64, 19.59, 19.58, 14.14.

HR-EIMS Calcd. for $C_{30}H_{49}FO_4$ 492.3615 (M^+), found 492.3616.

4.1.12. Preparation of 2-(7-fluoro-2-methyl-2-(4′,8′,12′-trimethyltridecyl)-chroman-6-yloxy) acetic acid **14**

The mixture of ethyl 2-(7-fluoro-2-methyl-2-(4′,8′,12′-trimethyltridecyl)-chroman-6-yloxy)-acetate **13** (0.22 g, 0.44 mmol) in THF (5 mL) and 10% KOH (15 mL) was stirred at room temperature for about 3 h, then the THF was evaporated, and the residue was neutralized with HCl to pH 1–2, extracted with CH_2Cl_2 (20 mL × 3), the combined CH_2Cl_2 were washed with water (20 mL × 2), and dried over $MgSO_4$. The solvent was evaporated and the residue was separated by silica gel column chromatography (19% ethyl acetate, 80% hexane, 1% HAc) to give the oil, 0.19 g, yield 95%. R_f 0.17 (19% ethyl acetate, 80% hexane, 1% HAc).

^{1}H NMR (δ/ppm, 600 M, $CDCl_3$), 0.82–0.85 (m, 12H, 4× CH_3), 1.02–1.17 (m, 7H), 1.18–1.42 (m, 14H), 1.47–1.59 (m, 3H), 1.69–1.73 (m, 1H), 1.76–1.81 (m, 1H), 2.61–2.69 (m, 2H), 4.62 (s, 2H, O$\underline{CH_2}$Ph), 6.53 (d, 1H, J = 12.40 Hz), 6.70 (d, 1H, J = 9.21 Hz).

^{13}C NMR (δ/ppm, 125 M, $CDCl_3$): 172.95, 152.96, 151.34, 149.80, 149.73, 138.55, 138.47, 118.28, 118.26, 116.55, 116.53, 105.72, 105.59, 76.57, 67.94, 67.93, 65.86, 39.94, 39.90, 39.38, 37.55, 37.54, 37.46, 37.45, 37.44, 37.41, 37.39, 37.36, 37.35, 37.29, 32.79, 32.78, 32.72, 32.70, 30.68, 30.65, 27.98, 25.58, 24.81, 24.80, 24.46, 23.99, 22.72, 22.62, 21.82, 21.02, 21.01, 21.00, 19.75, 19.68, 19.67, 19.66, 19.61, 19.60, 15.17.

HR-EIMS Calcd. for $C_{28}H_{46}FO_4$ 465.3380 $(M+1)^+$, found 465.3374.

4.1.13. Preparation of methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate **16a**, **16b**

To the mixture of (*R*)-Trolox **15b** (5.0 g, 20.0 mmol) in methanol (100 mL) and CH_2Cl_2 (20 mL), was added 4-methylbenzenesulfonic acid (PTSA) (1.0 g) at room temperature. Then the mixture was heated to reflux for 6 h. After cooling to room temperature, the reactant was concentrated to give a white solid, dissolved in ethyl acetate (120 mL), washed with saturated $NaHCO_3$ (80 mL × 2), water (80 mL × 1), successively, dried over $MgSO_4$. After the solvent was evaporated, the white solid was filtered and washed with hexane to give pure product **16b**, m.p. 131–132 °C, 5.1 g, yield 96%.

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 1.63 (s, 3H, 2-CH_3), 1.84–1.96 (m, 1H), 2.06 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.41–2.72 (m, 3H), 3.70 (s, 3H, CH_3), 4.33 (m, 1H, OH).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$) 174.76, 145.74, 145.54, 122.79, 121.54, 118.69, 117.10, 77.27, 52.62, 30.86, 25.68, 21.20, 12.46, 12.07, 11.49.

16a was obtained under the identical conditions with **15a**, white solid, m.p. 130–131 °C, yield 95%, ^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 1.62 (s, 3H, 2-CH_3), 1.83–1.94 (m, 1H), 2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.41–2.71 (m, 3H), 3.69 (s, 3H, CH_3).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$) 174.74, 145.71, 145.58, 122.73, 121.58, 118.62, 117.15, 77.22, 52.68, 30.83, 25.64, 21.23, 12.49, 12.02, 11.47.

4.1.14. Preparation of methyl 6-benzylchroman-2-carboxylate **17a**, **17b**

To the mixture of 2-(*R*)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate **16b** (5.0 g, 19 mmol) in 50 mL of DMF, was added K_2CO_3 (3.93 g, 28.5 mmol, 1.5 eq) under ice-bath. After the mixture was stirred for 20 min, benzyl bromide (3.89 g, 22.8 mmol, 1.2 eq) was added and the mixture was stirred at room temperature overnight. The reactant was diluted with 50 mL of water and 150 mL of ethyl acetate, the aqueous was extracted with ethyl acetate (50 mL × 2), the combined ethyl acetate phase were washed with water (1000 mL × 2), dried over Na_2SO_4. The solvent was removed off and the residue was separated by silica gel using eluent (10% ethyl acetate in hexane) to give white solid **17b**, m.p. 101–102 °C, 6.7 g, yield 95%, R_f 0.50 (10% EtOAc in hexane).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.67 (s, 3H, CH_3), 1.88–1.98 (m, 1H, 3-CH_2), 2.18 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.28 (s, 3H, CH_3),

2.45–2.72 (m, 3H, 3-CH_2, 4-CH_2), 3.74 (s, 3H, $COOCH_3$), 4.74 (s, 2H, CH_2Ph), 7.38–7.56 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 174.61, 149.12, 148.06, 138.22, 128.74, 128.56, 128.07, 127.96, 126.20, 123.20, 117.45, 77.44, 74.91, 52.64, 30.74, 25.71, 21.16, 13.17, 12.26, 12.16.

EI-MS for $C_{22}H_{26}O_4$ Calcd. 354 (M^+), found 356, 354, 295, 264, 263, 231.

17a, white solid, m.p. 101–102 °C, yield 94%, R_f 0.50 (10% EtOAc in hexane).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.63 (s, 3H, CH_3), 1.84–1.95 (m, 1H, 3-CH_2), 2.14 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.41–2.69 (m, 3H, 3-CH_2, 4-CH_2), 3.70 (s, 3H, $COOCH_3$), 4.70 (s, 2H, CH_2Ph), 7.35–7.52 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 174.67, 149.15, 148.09, 138.28, 128.71, 128.53, 128.05, 127.98, 126.26, 123.23, 117.48, 77.47, 74.95, 52.66, 30.78, 25.72, 21.18, 13.15, 12.24, 12.18.

EI-MS for $C_{22}H_{26}O_4$ Calcd. 354 (M^+), found 355 (M + 1), 295, 264, 263.

4.1.15. Preparation of (6-benzyloxy-2-methyl-chroman-2-yl) methanol *18a*, *18b*

To the precipitate of $LiAlH_4$ (0.67 g, 17.0 mmol) in 50 mL of dry THF, was added dropwise methyl 6-benzylchroman-2-carboxylate **17b** (2.0 g, 5.6 mmol) in 50 mL of dry THF under 0 °C with stirring. After addition, the mixture was stirred at 0 °C for 1 h, then warmed to room temperature for 2 h. After the TLC show there is no starting material, the reactant was quenched with saturated NH_4Cl aqueous under ice-bath, filtered and concentrated, then diluted with 80 mL of ethyl acetate, washed with brine (40 mL × 2), water (40 mL × 1), successively, dried over Na_2SO_4. The solvent was evaporated and the residue was separated by silica gel chromatography using hexane and ethyl acetate (V/V 3.5:1) as eluent to give an oil **18b**, 1.7 g, yield 93%, stood at room temperature for overnight to become a white solid, m.p. 71–72 °C, R_f 0.38 (25% EtOAc in hexane).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.29 (s, 3H, CH_3), 1.75–1.83 (m, 1H, 3-CH_2), 2.02–2.12 (m, 1H, 3-CH_2), 2.16 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.68–2.73 (m, 2H, 4-CH_2), 3.63–3.75 (q, 2H, J = 11.19 Hz, $\underline{CH_2}OH$), 4.75 (s, 2H, CH_2Ph), 7.36–7.57 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 148.88, 147.55, 138.14, 128.76, 128.52, 128.12, 128.01, 126.51, 123.19, 117.86, 75.64, 75.04, 69.64, 27.93, 20.83, 20.46, 13.16, 12.32, 12.20.

HR-EIMS for $C_{21}H_{26}O$ Calcd. 326.1882 (M^+), found 326.1883.

18a was obtained by the identical procedure.

18a: oil, stood at room temperature for a long time to become a white solid, m.p. 71–72 °C, yield 92%, R_f 0.29 (hexane/EtOAc V/V 5:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$): 1.27 (s, 3H, CH_3), 1.73–1.81 (m, 1H, 3-CH_2), 1.91–2.09 (m, 1H, 3-CH_2), 2.13 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.65–2.71 (m, 2H, 4-CH_2), 3.59–3.72 (m, 2H, $\underline{CH_2}OH$), 4.72 (s, 2H, CH_2Ph), 7.36–7.54 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 148.78, 147.50, 138.12, 128.66, 128.51, 128.13, 128.02, 126.48, 123.15, 117.85, 75.62, 75.01, 69.67, 27.96, 20.84, 20.47, 13.21, 12.31, 12.25.

HR-EIMS for $C_{21}H_{26}O$ Calcd. 326.1882 (M^+), found 326.1879.

4.1.16. Preparation of 6-benzyloxy-2-methyl-2-(3, 7, 11-trimethyl-dodecyloxy-methyl)-chroman *19a*, *19b* and *23*

After the mixture of 6-(benzyloxy-2-methyl-chroman-2-yl) methanol **18b** (0.8 g, 2.45 mmol) and NaH (60%, 0.5 g, 12.25 mmol, 5.0 eq) in 40 mL of dry THF was refluxed for 30 min, 1-bromo-3,7,11-trimethyldodecane **9** (0.87 g, 3.0 mmol) in 10 mL of dry THF was added and the mixture was constituted to reflux for 48 h. Then the mixture was cooled at room temperature and the solvent was evaporated under the reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with water (30 mL × 2), dried over $MgSO_4$. After the solvent was evaporated, the residue was separated by flash column chromatography on silica gel (hexane/EtOAc V/V 25:1) to give a colorless oil **19b**, 1.0 g, yield 76%, R_f 0.5 (hexane/EtOAc V/V 20:1).

^{1}H NMR (δ/ppm, 300 MHz, $CDCl_3$) 0.86–0.92 (m, 12H, 4× CH_3), 1.07–1.67 (m, 20H), 1.75–1.84 (m, 1H), 1.97–2.06 (m, 1H), 2.13 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.63 (t, 2H, J = 6.75 Hz, 4-CH_2), 3.39–3.62 (m, 4H, 2× CH_2O), 4.73 (s, 2H, CH_2Ph), 7.34–7.54 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 148.53, 147.96, 138.23, 128.71, 128.27, 128.03, 127.96, 126.27, 123.08, 117.97, 76.37, 75.25, 74.97, 70.64, 70.59, 39.63, 37.71, 37.69, 37.64, 37.61, 37.54, 37.04, 36.98, 36.96, 33.04, 30.18, 30.15, 28.79, 28.24, 25.08, 25.06, 24.64, 22.99, 22.89, 22.76, 20.60, 20.04, 20.01, 19.98, 19.93, 13.12, 12.27, 12.16.

HR-EIMS Calcd. for $C_{36}H_{57}O_3$ 537.4308 (M + 1)$^+$, found 537.4296.

19a and **23** were prepared by the identical procedure instead of **18a** and **5** as starting materials separately.

19a: colorless oil, yield 62%, R_f 0.45 (hexane/EtOAc V/V 20:1).

^{1}H NMR (δ/ppm, 300 MHz, $CDCl_3$) 0.91–0.95 (m, 12H, 4× CH_3), 1.11–1.48 (m, 17H), 1.52–1.81 (m, 4H), 1.97–2.06 (m, 1H), 2.70 (t, 2H, J = 6.71 Hz, 4-CH_2), 3.39–3.62 (m, 4H, 2× CH_2O), 5.08 (s, 2H, CH_2Ph), 6.62–6.75 (dd, 2H, J = 12.31, 9.23 Hz), 7.32–7.50 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 154.10, 150.86, 148.52, 148.38, 140.38, 140.23, 137.37, 128.76, 128.21, 127.80, 117.52, 117.48, 116.47, 116.42, 105.88, 105.60, 76.34, 76.04, 72.94, 70.60, 39.67, 37.73, 37.68, 37.64, 37.58, 36.94, 36.86, 33.07, 30.17, 28.64, 28.27, 25.12, 25.10, 24.67, 23.04, 22.94, 22.73, 22.71, 21.91, 20.05, 19.98.

HR-EIMS Calcd. for $C_{33}H_{49}FO_3$ 512.3666 (M + 1)$^+$, found 512.3663.

23: colorless oil, yield 67%, R_f 0.5 (hexane/EtOAc V/V 20:1), ^{1}H NMR (δ/ppm, 600 MHz, $CDCl_3$) 0.83–0.88 (m, 12H, 4× CH_3), 1.04–1.09 (m, 2H), 1.11–1.55 (m, 2H), 1.21–1.41 (m,12H), 1.48–1.64 (m, 4H), 1.74–1.78 (m, 1H), 1.95–2.00 (m, 1H), 2.09 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.59 (t, 2H, J = 6.79 Hz, 4-CH_2), 3.36–3.39 (dd, 1H, J = 7.63 Hz), 3.45–3.48 (dd, 1H, J = 7.45, 7.49 Hz), 3.49–3.58 (m, 2H), 4.69 (s, 2H, CH_2Ph), 7.31–7.50 (m, 5H, C_6H_5).

^{13}C NMR (δ/ppm, 125 M, $CDCl_3$): 148.34, 147.74, 138.03, 128.46, 128.03, 127.78, 127.72, 126.01, 122.86, 117.75, 117.74, 76.17, 76.16, 75.02, 75.02, 74.74, 70.42, 70.37, 39.40, 37.50, 37.49, 37.47, 37.45, 37.42, 37.38, 37.32, 36.84, 36.82, 36.77, 36.74, 32.82, 32.81, 29.98, 29.97, 29.95, 29.93, 28.60, 28.00, 24.84, 24.82, 24.82, 24.42, 24.41, 24.40, 22.74, 22.65, 22.54, 22.53, 20.37, 19.81, 19.78, 19.77, 19.74, 19.72, 19.70, 19.70, 12.88, 12.02, 11.91.

HR-EIMS Calcd. for $C_{36}H_{57}O_3$ 537.4308 (M + 1)$^+$, found 537.4294.

4.1.17. Preparation of 6-hydroxy-2-(3′,7′,11′-trimethyl-dodecyloxy methyl)-chroman *20a*, *20b* and *24*

The mixture of 6-benzyloxy-2,5,7,8-tetramethyl-2-(3′,7′,11′-trimethyl-dodecyloxymethyl)-chroman **19b** (0.8 g, 1.5 mmol) and 10% Pd/C in 25 mL of ethyl acetate was hydrogenated under 45 PSI for 24 h at room temperature. Then the reactant was filtered, concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc V/V 10:1) to give an oil **20b**, 0.56 g, yield 85%, R_f 0.40 (hexane/EtOAc V/V 10:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.88–0.92 (m, 12H, 4× CH_3), 1.07–1.43 (m, 17H), 1.51–1.71 (m, 3H), 1.75–1.84 (m, 1H), 1.96–2.07 (m, 1H), 2.15 (s, 6H, 2× CH_3), 2.19 (s, 3H, CH_3), 2.65 (t, 2H, J = 6.79 Hz, 4-CH_2), 3.38–3.65 (m, 4H, 2× CH_2O), 4.28 (brs, 1H, OH).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 145.60, 144.97, 122.76, 121.37, 118.78, 117.71, 76.31, 75.00, 70.63, 70.59, 39.64, 37.74, 37.71, 37.66, 37.62, 37.55, 37.07, 37.05, 36.99, 36.96, 33.06, 30.19, 30.16, 28.98, 28.25, 25.09, 25.08, 24.66, 23.00, 22.90, 22.65, 20.69, 20.02, 19.96, 19.94, 12.48, 12.12, 11.56.

HR-EIMS Calcd. for $C_{29}H_{50}O_3$ 446.3760 (M^+), found 446.3764.

20a and **24** were prepared by the identical procedure.

20a: yield 81%, R_f 0.22 (hexane/EtOAc V/V 10:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.86–0.91 (m, 12H, 4× CH_3), 1.05–1.45 (m, 17H), 1.49–1.78 (m, 4H), 1.94–2.03 (m, 1H), 2.68 (t, 2H, J = 6.67 Hz, 4-CH_2), 3.37–3.58 (m, 4H, 2× CH_2O), 5.18 (brs, 1H, OH), 6.54–6.70 (dd, 2H, J = 9.76, 11.82 Hz).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 151.64, 148.51, 147.30, 147.16, 137.01, 136.82, 117.34, 117.29, 117.06, 117.02, 104.86, 104.58, 76.27, 76.04, 70.65, 39.62, 37.67, 37.63, 37.59, 37.53, 36.84, 36.76, 33.03, 30.11, 28.61, 28.23, 25.07, 25.05, 24.62, 22.98, 22.89, 22.53, 22.51, 21.74, 19.98, 19.92.

HR-EIMS Calcd. for $C_{26}H_{43}FO_3$ 423.3274 (M + 1) $^+$, found 423.3268.

24: yield 96%, R_f 0.40 (hexane/EtOAc V/V 10:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.86–0.91 (m, 12H, 4× CH_3), 1.05–1.45 (m, 17H), 1.49–1.68 (m, 3H), 1.74–1.83 (m, 1H), 1.95–2.04 (m, 1H), 2.14 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.64 (t, 2H, J = 6.82 Hz, 4-CH_2), 3.37–3.63 (m, 4H, 2× CH_2O), 4.24 (brs, 1H, OH).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 145.59, 144.95, 122.77, 121.32, 118.74, 117.72, 76.30, 75.00, 70.62, 70.58, 39.63, 37.72, 37.69, 37.64, 37.61, 37.54, 37.06, 37.04, 36.98, 36.95, 33.04, 30.17, 30.14, 28.97, 28.24, 25.06, 25.07, 24.63, 22.99, 22.89, 22.63, 20.68, 20.00, 19.96, 19.93, 12.47, 12.11, 11.55.

HR-EIMS Calcd. for $C_{29}H_{50}O_3$ 446.3760 (M^+), found 446.3764.

*4.1.18. Preparation of ethyl 2-(2-methyl-2-((3′,7′,11′-trimethyldodecyloxy)-methyl) chroman-6-yloxy)acetate **21a**, **21b** and **25***

To the mixture of 6-hydroxy-2,5,7,8-tetramethyl-2-(3′,7′,11′-trimethyl-dodecyloxymethyl)-chroman **20b** (0.36 g, 0.8 mol) in DMF (10 mL), was added ethyl bromoacetate (0.16 g, 0.97 mmol), and then powder NaOH (48 mg, 1.2 mmol) was added, the mixture was stirred at room temperature until there is no starting material and diluted with ethyl acetate (50 mL) and brine (30 mL), the aqueous was extracted with ethyl acetate (20 mL × 2), the combined ethyl acetate were washed with brine (30 mL × 2), water (30 mL × 1), dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (hexane/ethyl acetate V/V 10:1) to give the colorless oil **21b**, 0.4 g, yield 95%, R_f 0.45 (hexane/EtOAc V/V 10:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.86–0.92 (m, 12H, 4× CH_3), 1.07–1.42 (m, 20H), 1.48–1.67 (m, 3H), 1.73–1.82 (m, 1H), 1.95–2.04 (m, 1H), 2.09 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.61 (t, 2H, J = 6.85 Hz, 4-CH_2), 3.37–3.61 (m, 4H, 2× CH_2O), 4.25–4.36 (m, 4H).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 169.60, 148.25, 148.21, 127.89, 125.93, 123.17, 118.00, 76.34, 75.29, 70.62, 70.57, 70.26, 61.31, 39.62, 37.70, 37.67, 37.63, 37.60, 37.53, 37.02, 36.96, 36.94, 33.03, 30.16, 30.14, 28.70, 28.23, 25.07, 25.05, 24.63, 22.98, 22.88, 22.73, 20.53, 20.02, 20.00, 19.96, 19.93, 14.48, 12.99, 12.13, 12.11.

HR-EIMS Calcd. for $C_{33}H_{56}O_5$ 532.4128 (M^+), found 532.4128.

21a and **25** were prepared by the identical procedure.

21a: oil, yield 89%, R_f 0.60 (hexane/EtOAc V/V 10:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.85–0.89 (m, 12H, 4× CH_3), 1.00–1.43 (m, 20H), 1.46–1.67 (m, 3H), 1.69–1.78 (m, 1H), 1.93–2.02 (m, 1H), 2.67 (t, 2H, J = 6.6 Hz, 4-CH_2), 3.34–3.56 (m, 4H, 2× CH_2O), 4.23–4.30 (q, 2H, J = 7.14 Hz, O$\underline{CH_2}$$CH_3$), 4.60 (s, 2H, CH_2O), 6.55–6.73 (dd, 2H, J = 12.42, 9.23 Hz).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$), 169.34, 154.01, 150.77, 149.35, 149.22, 139.46, 139.31, 118.40, 118.36, 116.67, 116.62, 105.92, 105.64, 76.46, 75.98, 70.58, 68.49, 68.46, 61.47, 39.60, 37.67, 37.64, 37.61, 37.58, 37.51, 36.87, 36.78, 33.01, 30.11, 28.49, 28.21, 25.05, 25.03, 24.60, 22.96, 22.87, 22.65, 22.63, 21.80, 19.97, 19.91, 14.39.

HR-EIMS Calcd. for $C_{30}H_{49}FO_5$ 508.3564 (M^+), found 508.3568.

25: oil, yield 73%, R_f 0.36 (hexane/EtOAc V/V 15:1).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.85–0.91 (m, 12H, 4× CH_3), 1.05–1.43 (m, 20H), 1.48–1.66 (m, 3H), 1.73–1.82 (m, 1H), 1.94–2.03 (m, 1H), 2.09 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.59 (t, 2H, J = 6.79 Hz, 4-CH_2), 3.36–3.60 (m, 4H, 2× CH_2O), 4.27–4.36 (m, 4H).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 169.61, 148.25, 148.20, 127.89, 125.93, 123.17, 118.00, 76.34, 75.29, 70.62, 70.58, 70.25, 61.31, 39.62, 37.70, 37.67, 37.63, 37.59, 37.52, 37.02, 36.96, 36.93, 33.03, 30.16, 30.14, 28.69, 28.22, 25.07, 25.05, 24.63, 22.97, 22.88, 22.72, 20.52, 20.02, 19.99, 19.95, 19.92, 14.47,, 12.98, 12.12, 12.10.

HR-EIMS Calcd. for $C_{33}H_{56}O_5$ 532.4128 (M^+), found 532.4126.

*4.1.19. Preparation of 2-(2-methyl-2-((3′,7′,11′-trimethyldodecyloxy)-methyl)-chroman-6-yloxy)-acetic acid **22a**, **22b** an **26***

The mixture of ethyl 2-(2-methyl-2-(4′,8′,12′-trimethyl-tridecyl)-chroman-6-yloxy)-**21b** (0.45 g, 0.84 mmol) in THF (10 mL) and 10% KOH (30 mL) was stirred at room temperature for about 3 h, then the THF was removed off, and the residue was neutralized with HCl to pH 1–2, extracted with CH_2Cl_2 (20 mL × 3), the combined CH_2Cl_2 were washed with water (20 mL × 2), and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by column chromatography (19% ethyl acetate, 80% hexane, 1% HAc) to give the oil. The oil was dissolved in 30 mL of CH_2Cl_2 again, washed with water (10 mL × 30), dried over $MgSO_4$, then the solvent was removed off to give the oil **22b**, 0.4 g, yield 95%, R_f 0.27 (19% ethyl acetate, 80% hexane, 1% HAc).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.85–0.91 (m, 12H, 4× CH_3), 1.03–1.44 (m, 17H), 1.48–1.69 (m, 3H), 1.74–1.82 (m, 1H), 1.95–2.04 (m, 1H), 2.10 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.61 (t, 2H, J = 6.78 Hz, 4-CH_2), 3.38–3.58 (m, 4H, 2× CH_2O), 4.38 (s, 2H).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 173.56, 148.56, 147.44, 127.68, 125.76, 123.43, 118.17, 76.33, 75.42, 70.68, 70.65, 69.41, 39.62, 37.69, 37.66, 37.63, 37.60, 37.53, 36.99, 36.92, 36.90, 33.03, 30.16, 30.14, 28.62, 28.23, 25.07, 25.05, 24.62, 22.97, 22.88, 22.62, 20.52, 19.99, 19.92, 12.98, 12.12.

HR-EIMS Calcd. for $C_{31}H_{52}O_5$ 504.3815 (M^+), found 504.3817.

22a and **26** were prepared by the identical procedure.

22a, oil, yield 96%, R_f 0.20 (19% ethyl acetate, 80% hexane, 1% HAc).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.85–0.89 (m, 12H, 4× CH_3), 1.04–1.43 (m, 17H), 1.49–1.66 (m, 3H), 1.71–1.78 (m, 1H), 1.94–2.03 (m, 1H), 2.69 (t, 2H, J = 6.67 Hz, 4-CH_2), 3.37–3.57 (m, 4H, 2× CH_2O), 4.65 (s, 2H), 6.56–6.74 (dd, 2H, J = 12.38, 9.19 Hz), 9.44 (brs, 1H, COOH).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 174.29, 153.92, 150.68, 149.59, 149.45, 139.09, 138.94, 118.32, 118.29, 116.83, 116.78, 106.04, 105.76, 76.58, 75.99, 70.67, 67.94, 39.60, 37.67, 37.64, 37.61, 37.58, 37.51, 36.83, 36.74, 33.01, 30.11, 28.43, 28.22, 25.05, 25.04, 24.61, 22.97, 22.88, 22.54, 22.51, 21.77, 19.98, 19.91.

HR-EIMS Calcd. for $C_{28}H_{45}FO_5$ 480.3251 (M^+), found 480.3250.

26, oil, yield 93%, R_f 0.27 (19% ethyl acetate, 80% hexane, 1% HAc).

^{1}H NMR (δ/ppm, 300 M, $CDCl_3$), 0.86–0.92 (m, 12H, 4× CH_3), 1.05–1.46 (m, 17H), 1.49–1.70 (m, 3H), 1.75–1.83 (m, 1H), 1.96–2.05 (m, 1H), 2.11 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.61 (t, 2H, J = 6.57 Hz, 4-CH_2), 3.40–3.62 (m, 4H, 2× CH_2O), 4.39 (s, 2H), 9.80 (brs, 1H, COOH).

^{13}C NMR (δ/ppm, 75 M, $CDCl_3$): 174.12, 148.49, 147.59, 127.73, 125.81, 123.38, 118.11, 76.33, 75.41, 70.72, 70.68, 69.45, 39.63, 37.70, 37.64, 37.60, 37.54, 36.98, 36.91, 36.89, 33.03, 30.16, 30.13, 28.63, 28.23, 25.08, 25.06, 24.63, 22.99, 22.89, 22.58, 20.52, 20.00, 19.93, 12.98, 12.12.

HR-EIMS Calcd. for $C_{31}H_{52}O_5$ 505.3893 (M + 1)$^+$, found 505.3893.

4.2. Biological assay methods

4.2.1. Cell culture and reagents

The source and culture conditions for 66cl-4GFP murine mammary tumor cells are previously described [52]. MDA-MB-231 and MCF-7 human breast cancer cells were obtained from the American Type Culture Collection (ATCC), cultured and maintained in MEM medium as previously described [17,19]. Cells were maintained in MEM medium supplemented with 10% fetal bovine serum (FBS) (HyClone Laboratories, Logan, UT, USA), 2 mM glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin, 1 × MEM non-essential amino acid solution (Sigma) and 2 × MEM vitamins solution (Sigma). For experiments, FBS was reduced to 2% to better mimic the *in vivo* low serum exposure of these cancer cells.

Vitamin E compounds were dissolved in DMSO at 40 mM as stock solution. DMSO was used as vehicle control (VEH) at levels equivalent to the highest dose of vitamin E compounds used in a given experiment.

4.2.2. Evaluation of apoptosis

Apoptosis was quantified using the Annexin V-PE assay following the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA). This assay measures amount of phosphatidylserine on the outer surface of the plasma membrane (a biochemical alteration unique to membranes of apoptotic cells). Fluorescence was measured using FACS Calibur flow cytometry and data were analyzed using CellQuest software (BD Biosciences, San Jose, CA, USA). Cells displaying phosphatidylserine on their surface (positive for Annexin-V fluorescence) were considered to be apoptotic [53].

4.2.3. Western blot analyses

Western blot analyses to assess protein levels in whole cell extracts were performed as described previously [19]. Antibodies to poly (ADP-ribose) polymerase (PARP) and Survivin were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Following transfer, blots were reacted with primary antibody in 0.1% BSA/TBST overnight at 4 °C, washed three times with TBST, and reacted with horseradish peroxidase-conjugated goat anti-rabbit or rabbit anti-mouse (Jackson Immunoresearch, Rockford, IL, USA) secondary antibodies.

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