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Graphical abstract

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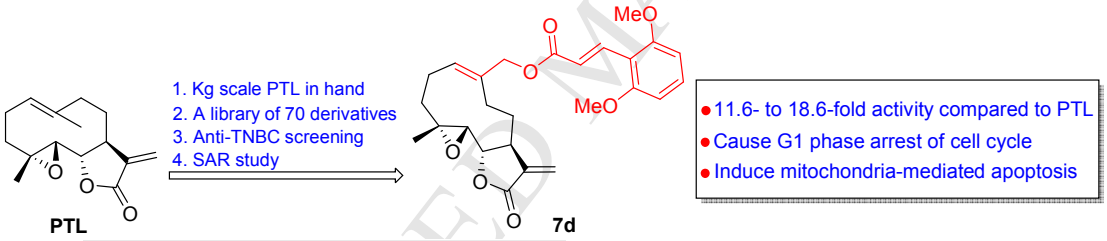

Cells	IC_{50} (μM)	
	PTL	7d
MDA-MB-231	3.48	0.25
SUM-159	3.06	**0.20**
MCF-7	2.68	0.23
Bcap-37	4.63	0.27
4T1	4.09	0.22

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ABSTRACT

Triple-negative breast cancer (TNBC) is the most aggressive cancers with a high recurrence rate and rapidly acquired drug resistance among various breast cancer subtypes. There is no specific drug for treatment of TNBC. Discovery of therapeutic agents with unique modes of actions is urgently needed. In this study, a series of seventy parthenolide derivatives was designed, synthesized, and evaluated for their anti-TNBC activities. Compound **7d** exhibited the most potent activity against different breast cancer cells with IC_{50} values ranging from 0.20 μM to 0.27 μM, which demonstrated 11.6- to 18.6-fold improvement comparing to that of the parent compound parthenolide with IC_{50} values of 2.68–4.63 μM. It is worth to note that **7d** was more active than the positive control drug ADR. Moreover, compound **7d** could induce apoptosis of SUM-159 cells through mitochondria pathway and cause G1 phase arrest of SUM-159 cells. These findings indicate that compound **7d** deserves further studies as a lead compound for ultimate discovery of effective anti-TNBC drug.

KEYWORDS

Parthenolide; Structure-activity relationship; Triple negative breast cancer; Apoptosis; Cell cycle

1. INTRODUCTION

Breast cancer is the most common cancer and the second leading cause of cancer-related mortality among women in the world [1-3]. Every year, an estimated 1 to 1.3 million breast cancer cases are diagnosed worldwide [4]. Triple-negative breast cancer (TNBC) is characterized by lack of expression of human epidermal growth factor receptor 2 (HER-2), estrogen receptor (ER), and progesterone receptor, which accounts for approximately 15–20 % of breast cancer cases, and more frequent in African-American younger women and BRCA1 mutation carriers. [5-7]. TNBC is the most aggressive cancers with a high recurrence rate and rapidly acquired drug resistance among various breast cancer subtypes [8-10]. TNBC could increase lymphocytic infitration, and have large tumor size. TNBCs are associated with a 4-fold increase in the risk of distant metastases [11]. TNBCs metastasize to the lungs and central nervous system more frequently than non-TNBCs, which most commonly metastasize to the bone [12, 13]. This aggressive metastatic behavior contributes to the overall shortened survival of patients with TNBC compared with non-TNBC. Because of the lack of appropriate targets, TNBC patients couldn't benefit from molecularly targeted therapy, such as endocrine therapy or trastuzumab. Cytotoxic chemotherapy (i.e., taxanes, anthracyclines, capecitabine, ixabepilone) is the only standard of care therapeutic choice for patients presenting with metastatic TNBC [14-16]. Although these patients respond to chemotherapeutic agents such as taxanes and anthracyclines better than other subtypes of breast cancer, prognosis remains poor. The reason is that although the initial chemotherapy results are significant, it is limited by dose-related toxic factors and acquired chemoresistance, it is difficult to guarantee the chemotherapy cycle, which leads to recurrence finally [17, 18]. Therefore, discovering therapeutic agents with unique modes of actions is urgently needed to overcome current challenges in TNBC treatment.

Sesquiterpenes lactones (SLs) have attracted extensive attention because of their potent bioactivity, such as anti-cancer, anti-inflammatory and anti-malaria [19-21]. Parthenolide (**1**, PTL, Figure 1), a prominent germacrane type SL, showed promising anti-cancer property. Nevertheless, PTL has some disadvantages, such as poor oral bioavailability, lack of stability under chemical and physiological conditions and poor water solubility [22-25]. DMAPT (dimethylaminoparthenolide), a prodrug of PTL, effectively increased the water solubility and oral bioavailability, which has advanced into a phase I clinical trial for treatment of acute myeloid leukemia (AML) [21]. Recently, we developed the other PTL derivative, ACT001 [23], to be in clinical trial in Australia and China for treatment of glioblastoma [26].

Cinnamic acid (CA) is a naturally occurring aromatic fatty acid composed of a phenyl ring substituted with an acrylic acid group, which has a long history of being used as a plant flavourings and spices [27-28]. Cinnamic acid (CA) and cinnamic acid derivatives (CADs) were found abundantly in many plants and food, exhibited a broad spectrum of biological activities, including anticancer, antioxidant, antimicrobial, antiviral antiinflmmatory, hepatoprotective and hypolipidemic [29-32]. CADs possesses an α,β-unsaturated carbonyl, which can be considered as a Michael acceptor, an active structural unit often appeared in the design of drugs [33-35]. CA scaffflds are present in several registered drugs, such as Panobinostat (antitumor drug) and cinanserin and tranilast (antiallergic drugs) [36-38]. Anticancer potential of CADs has been known for more than a century [39]. The antitumor activities of various cinnamic acid derivatives has attracted the interest of many research teams. Particularly, cinnamic acid ester derivatives can significantly increase antitumor activity [40-43]. There are many studies reported that it could generate ROS to induce apoptosis [44-46].

In this study, with PTL as the starting point, we developed a series of PTL derivatives, investigated their biological activities as potential anti-TNBC agents, and discussed the structure−activity relationship (SAR), which led to the discovery of the most potent compound **7d**. The preliminary mechanism of **7d** was also investigated.

2. RESULTS AND DISCUSSION

2.1 Chemistry

It was reported that the starting material parthenolide was obtained from feverfew (*Tanacetum parthenium*) in yield of only 0.14–0.74% [47]. We discovered that parthenolide could be readily crystallized in approximately 5% yield from the extract of root bark of *Magnolia delavayi* without chromatography. With abundant PTL (kilogram scale) in hand, we started the synthesis of PTL derivatives. PTL was converted to melampomagnolide B (MMB, **2**) following the procedure reported by our group [48]. The primary hydroxyl of MMB would be efficiently modified to improve its potency and to study the SAR. As described in Scheme 1, MMB conjugated with cinnamic acid or difference patterns of mono-substituted cinnamic acids to generate derivatives **4a**–**4x**, which could be evaluated for their anti-TNBC activity to explore the influence of different substituents of the benzene ring on their anti-TNBC activity. When phenolic hydroxyl groups of cinnamic acid derivatives were used, the yield of the esterification reaction was very low under the generally used condition (EDCI, DMAP, and TEA in CH_2Cl_2). We proposed that phenolic hydroxyl group was more reactive than the primary hydroxyl of MMB under used condition (EDCI, DMAP, and TEA in CH_2Cl_2), which led to self-esterification for substituted cinnamic acids containing phenolic hydroxyl groups. Finally, we utilized the Mitsunobu reaction, DIAD and PPh_3 in THF, to prepare **5a** and **5b** in yields of 76% and 55%,

respectively. In order to further investigate the effects of phenyl group in cinnamic acid, we designed the derivatives with replacement of the phenyl group in cinnamic acid with heterocyclic rings (**6a**–**6e**), naphthalene ring (**6f**), or benzodioxole ring (**6g**). As shown in Scheme 2, compounds **6a, 6b, 6f and 6g** was readily prepared in the presence of EDCI, DMAP, and TEA in high yields of 82%–95%. However, for the pyridinylacrylic acids, no reaction was observed under EDCI, DMAP, and TEA condition, which would attribute to the low reactivity of the ester intermediate. The pyridinylacrylic acids were firstly converted to the corresponding acyl chloride and then reacted with MMB to yield compounds **6c**–**6e** in yields of 66%–77%. MMB was reacted with commercial available di-methoxyl, tri-methoxyl or di-halo substituted cinnamic acids to give derivatives **7a**–**7m** (Scheme 3).

To investigate the effect of 17-substitutents of cinnamyl moiety on the anti-TNBC activity, derivatives **10a**–**10i**, **12a**–**12c** and **14** were designed, as shown in Scheme 4. We used **8a** as the starting material by Knoevenagel reaction to prepare a series of 17-substitued cinnamic acids **9a**–**9i**, **11a**–**11c** and **13**, followed by direct esterification with MMB to generate derivatives **10a**–**10i**, **12a**–**12c** and **14**.

Preliminary study indicated that compounds **7c** and **7d** showed high activity against MDA-MB-231 cells. Both of two derivatives have two α, β-unsaturated ester moieties. In order to explore the effects of these two α, β-unsaturated ester moieties on their anti-TNBC activities, we designed compound **16** with trim of the double bond of cinnamyl moiety, compounds **20a** and **20b** with reduction of the double bonds of *γ*-butyrolactone moiety, and compounds **21a** and **21b** with reduction of the double bonds of cinnamyl moiety (Scheme 5). Compound **16** was synthesized by esterification of MMB and 2, 6-dimethoxybenzoic acid in 83% yield. Reduction of MMB with sodium borohydride in an ice-water bath generated alcohol **15**. Aldehydes **8a** and

8b were through Knoevenagel reaction to provide the corresponding α, β-unsaturated acids **17a** and **17b**. Reaction of alcohol **15** with α, β-unsaturated acids **17a** and **17b** afforded esters **20a** and **20b**, respectively. Reduction of the α, β-unsaturated acids **17a** and **17b** with H_2, Pd/C afforded acids **18a** and **18b**, which were subsequently coupled with MMB to produce esters **21a** and **21b**, respectively. To study the effect of ten-membered skeleton of PTL moiety, compounds **19a** and **19b** were also synthesized.

The details of the synthetic procedures and structural characterizations are described in the Experimental Section. The assignment of the NMR spectra was also provided in Experimental Section. The purity of all PTL derivatives was confirmed to be ≥95% by HPLC.

2.2 The antiproliferative activity of parthenolide derivatives against breast cancer cells

The *in vitro* antiproliferative efficacy of the parthenolide derivatives **3**, **4a**–**4x** and **5a**–**5b** was determined by the MTT assay using human breast cancer cell line MDA-MB-231 and compared with the reference compounds, PTL (**1**) and MMB (**2**). In addition, adriamycin (ADR), the clinically used drug, was introduced as a positive control.

As shown in Table 1, the natural product PTL (**1**, IC_{50} = 3.48 μM) and MMB (**2**, IC_{50} = 5.59 μM) exhibited moderate activity against the MDA-MB-231 cells. Generally, all the tested twenty-seven derivatives **3**, **4a**–**4x** and **5a**–**5b** in Table 1 were more potent than PTL and MMB against the MDA-MB-231 cells, which indicated that the introduction of cinnamyl or substituted cinnamyl moiety was beneficial to anti-TNBC activity. Compound **3** (IC_{50} = 1.35 μM) with introduction of cinnamyl moiety exhibited two-fold anti-TNBC activity compared to PTL (IC_{50} = 3.48 μM). Different patterns of substituents were induced to the *ortho*-position of the benzene ring provided compounds **4a**–**4g**. Among them, three compounds **4a**, **4f**, **4g** showed high activity

with IC_{50} values lower than 1 μM. Introduction of halogen atoms (**4b**–**4d**) or methyl group (**4e**), with IC_{50} values ranging from 1.33 μM to 1.80 μM, slightly increased the anti-TNBC activity compared with PTL. Compound **4a** with the strong electron-withdrawing group trifluoromethyl exhibited further improved activity (IC_{50} = 0.74 μM). When the electron-donating group methoxy group (**4f**, IC_{50} = 0.46 μM) and ethoxyl group (**4g**, IC_{50} = 0.34 μM) were introduced, the activity was further enhanced. Especially, compound **4g** was about 10-fold more efficacious than PTL for MDA-MB-231 cells. The above results indicate that the introduction of an electron-donating group at the *ortho*-position of the benzene ring is beneficial to the antiproliferative potency. Compounds **4h**–**4m**, introducing different substituents at the *meta*-position of the phenyl ring, exhibited comparable or decreased activity comparing with their *ortho*-position counterparts **4a**–**4f**, respectively. The anti-TNBC activities of compounds **4n**–**5a**, which introduced different substituents at the *para*-position of the phenyl ring, were slightly enhanced in comparison with PTL. Compound **5b** showed moderate activity with IC_{50} value of 2.01 μM.

To investigate the effect of phenyl group in compound **3**, we synthesized compounds **6a**–**6g** with replacement of phenyl group with different aromatic rings. Their activities were shown in Table 2. These compounds showed comparable or slightly decreased activity compared with compound **3**.

Based on the above preliminary results, we decided to further explore the influence of different substituents on phenyl ring of compound **3**. Compounds **7a**–**7m** were synthesized and evaluated against MDA-MB-231 cells, and the results are shown in Table 3. Among subseries of **7a**–**7f** with dimethoylphenyl moiety, compounds **7b**, **7c** and **7d** showed improved activity compared to compound **3**. The activity was in the order of 2,6 (**7d**) > 2,5 (**7c**) > 2,4 (**7b**) > 2,3 (**7a**) > 3,4 (**7e**) > 3,5 (**7f**). Importantly, compounds **7c** and **7d** exhibited significantly inhibitory

activity against the MDA-MB-231 cells with IC_{50} values of 0.26 μM and 0.25 μM, respectively, which was approximately 14-fold and 22-fold more potent than PTL (IC_{50} = 3.48 μM) and MMB (IC_{50} = 5.596 μM), respectively. It is worth to note that compounds **7c** and **7d** were more active than the positive control drug ADR (IC_{50} = 0.8 μM). When three methoxy groups were introduced (compounds **7g**–**7j**), except for **7g** (IC_{50} = 1.77 μM), the antiproliferative activity of **7h**–**7j** was slightly improved with IC_{50} values ranging from 0.95 μM to 1.09 μM in comparison with compound **3** (IC_{50} = 1.35 μM). Taking account that compound **7d** with two methoxy groups at 2,6-positions of benzene ring, compound **7k**–**7m**, replacing of two methoxy groups with 2, 6-dihalogen, were also synthesized and evaluated for their anti-TNBC activity. However, the replacements led to decreased activities (IC_{50} = 1.50–1.59 μM) compared to **7d** (IC_{50} = 0.25 μM).

After investigating the effect of substituents on the benzene ring of cinnamyl moiety, we focused our attention on the double bond of cinnamyl moiety. Compound **7c** was selected as the basic skeleton. We designed to introduce different patterns of substituents on 17-position of the cinnamyl moiety, such as phenyl, substituted phenyl, alkyl and cyano, i.e. compounds **10a**–**10i**, **12a**–**12c** and **14**. Their suppressant properties on MDA-MB-231 cells were evaluated, and the results are shown in Table 4. The introduction of a phenyl group (**10a**) or substituted phenyl group (**10b**–**10i**) seriously reduced anti-TNBC activity (IC_{50} = 1.87 μM–2.95 μM) comparing with their parent compound **7c** (IC_{50} = 0.26 μM). For compounds **12a**–**12c**, the results suggested that the introduction of alkyl chains on the double bond resulted in a decrease in activity, and as the increase of chain length, activity decreased significantly. Compound **14**, with introduction of an electron-withdrawing cyano group into the double bond, also showed a 9-fold decrease in

comparison with **7c**. The above results demonstrated that 17-position of the cinnamyl moiety cannot accommodate diverse modification.

Finally, to investigate the contribution of each α, β-unsaturated ester bonds and further study the SAR, we designed compounds **16**, **20a**–**b** and **21a**–**b** with elimination of one of double bond. To indicate the importance of 10-membered ring, esters **19a**–**b** were also synthesized and evaluated for their anti-cancer activity. Compound **16**, with trim of the double bond of cinnamyl moiety in compound **7d**, reduced by 14.2 folds compared to **7d** (**16**: IC_{50} = 3.55 μM vs **7d**: IC_{50} = 0.25 μM), which demonstrated the significance of the double bond for its activity. When the double bond of cinnamyl moeity was reduced, i.e. compounds **21a** (IC_{50} = 1.88 μM) and **21b** (IC_{50} = 2.30 μM), their activities were also significantly reduced in comparison with **7c** and **7d**, respectively, but slightly stronger than PTL (IC_{50} = 3.48 μM). Similarly, when the double bond of the γ-butyrolactone ring of PTL was reduced, i.e. compounds **20a** (IC_{50} = 6.80 μM) and **20b** (IC_{50} = 7.6 μM), their potency was greatly decreased compared to **7d**. It is worth to note that **21a** and **21b** were more potent than **20a** and **20b**, respectively, which prompted us to propose that α-methylene-γ-butyrolactone fragment is more significant than the cinnamyl moiety. Esters **19a** (IC_{50} > 50 μM) and **19b** (IC_{50} > 20 μM) lost anti-TNBC activity. Moreover, as shown in Figure 2, compounds **17b** (IC_{50} > 50 μM) and MMB (IC_{50} = 5.59 μM) or combination of **17b** and MMB (1:1) (IC_{50} = 3.92 μM) were less potent than **7d** (IC_{50} = 0.25 μM). These results suggest that the anti-TNBC activity of **7d** may be attributed to the synergic effects of MMB part and cinnamyl moiety.

Compounds **4a**, **4f**, **4g**, **4h**, **7b**–**7d** and **7j**, exhibiting high activity against MDA-MB-231 cells lower than 1 μM ranging from 0.25 μM to 0.95 μM, were selected to further characterize their anti-breast cancer activity. These compounds were evaluated against a panel of three human

breast cancer cell lines, including SUM-159, MCF-7, Bcap-37, and a mouse breast cancer cell line 4T1. As shown in Table 6, compound **7d** exhibited the most potent activity against breast cancer cells with IC_{50} values ranging from 0.20 μM to 0.27 μM, which demonstrated 11.6- to 18.6-fold improvement comparing to that of the parent compound PTL.

The most potent compound **7d** was further evaluated for its toxicity against normal 3T3 cells (mouse embryonic fibroblast cell line). As shown in Table 7, **7d** had selective cytotoxicity against breast cancer cells (IC_{50} = 0.22 μM) being compared with 3T3 cells (IC_{50} = 8.13 μM) with therapeutic index (TI) value of 36.9. In contrast, the clinically used drug ADR showed toxicity against 3T3 cells with IC_{50} value of 0.36 μM, which led to low therapeutic index value of 0.45.

*2.3 Cell cycle effect of compound **7d***

To further analyze the effect of compound **7d** in cell proliferation, cell cycle distribution was detected by flow cytometry. From the result of Figure 3, S phase and G2/M phase were strongly decreased after the treatment of compound **7d** for 48 hours, while G1 phase was significantly increased with **7d** treatment compared with control group. As shown in Figure 4, the cell cycle related proteins including CHK2, p-CHK2, CHK1, p-CHK1 and p-cdc2 were down regulated, whereas the cell cycle inhibitor P27 were up-regulated after **7d** treatment for 48 hours.

*2.4 Compound **7d** induced apoptosis through mitochondria-mediated pathway*

In order to analyze the effect of compound **7d**, the cell apoptosis assay was performed by Annexin V/PI staining. The percentage of apoptosis cells was the sum of early apoptosis (annexin V^+/PI^-) and late apoptosis (annexin V^-/PI^-). As shown in Figure 5, the percentage of cell

apoptosis was 3.1±1.0, 2.9±1.0 and 26.0±7.4 with the treatment of compound **7d** at the concentration of 0, 0.2 μM and 0.5 μM respectively. Moreover, compound **7d** exhibited significant stronger effect on induction of cell apoptosis compared with that of PTL (Figure 5). It was reported that mitochondria-mediated apoptosis played important roles in anti-cancer drug discovery. Therefore, we wondered that whether compound **7d** induced cell apoptosis by mitochondria. As shown in Figure 6, the relative levels of apoptotic protein Bax and Bim was dramatically increased with a dose-dependent manner. Bax and Bim are important mitochondrial protein which regulated the release of cytochrome C. Moreover, compound **7d** induced the cytochrome C release and the cleavage of caspase 9 to induce cell apoptosis (Figure 6). These results above suggested that compound **7d** induced mitochondria-mediated apoptosis by the regulation of the proteins on the mitochondria.

*2.5 Reaction of Compound **7d**, **20b** and **21b** with GSH*

Covalent drugs can possess advantages over traditional non-covalent inhibitors, such as exceptionally high efficiency, longer duration of action [49]. Thirty-nine covalent drugs have been approved by the U.S. FDA from 1982−2009 [50]. The GSH conjugation assay was utilized for determination of intrinsic reactivity of electrophilic warhead. The reactivity of GSH with the covalent drugs was assessed to correlate the intrinsic reactivities of the covalent inhibitors with the biologically relevant covalent binding [51-53]. To determine the experimental GSH reaction rates of PTL derivatives, compounds **7d**, **20b** and **21b** were incubated with 2.5–3 equiv of GSH in 0.5 mL of DMSO-*d*6 and 0.05 mL of sodium phosphate deuterium oxide buffer (pH 7.4) at 37 °C. The reaction mixture was run ^{1}H NMR at different points (Figure 7). The results indicated that the reactivity of the covalent warhead α-methylene-γ-butyrolactone in **7d** is much more active than the enone in cinnamyl moiety. Additionally, the adduct product **25** was also validated

by HRMS analysis. Under the same conditions, **21b** could reacted with GSH (Figure 8), and no reaction was observed for compound **20b** (Figure 9).

3. CONCLUSIONS

TNBC is the most aggressive cancers among various breast cancer subtypes. It is still a great challenge in clinical treatment. Therefore, discovery of potential novel agents for treatment of TNBC is still urgently needed. We designed, synthesized, and identified a series of parthenolide derivatives as potential anti-TNBC agents, especially compound **7d** exhibited IC_{50} values ranging from 0.20 μM to 0.27 μM, which was 11.6- to 18.6-fold more potent than that of the parent compound PTL with IC_{50} values of 2.68 μM–4.63 μM for a panel of five different breast cancer cells. Further characterization indicated that compound **7d** could induce apoptosis of SUM-159 cells through mitochondria pathway and cause G1 phase arrest of SUM-159 cells. These findings indicate that compound **7d** deserves further studies as a lead compound for ultimate discovery of effective anti-TNBC drug.

4. EXPERIMENTAL SECTION

4.1 General Chemistry

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. The used solvents were purified and dried according to common procedures. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Tsingdao silica gel plates (60F-254). Visualization was achieved using UV light, phosphomolybdic acid in ethanol or potassium permanganate in water, each followed by heating. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column

chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded with a Bruker 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer and referenced to the solvent peak for $CDCl_3$, CD_3OD and DMSO-d_6. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. The purity of the final compounds was determined to be ≥ 95% by means of Ultimate 3000 analytical high performance liquid chromatography (HPLC) with an C18 column (4.6 × 150 mm, 5 μm, Thermofisher) eluted at 1 mL/min with Milli-Q water and CH_3CN. HRMS (ESI) spectra were recorded with a VG ZAB-HS chromatography-mass spectrometer.

*4.1.1 Synthesis of melampomagnolide B (**2**)*

A solution of **1** (1.0 g, 4.3 mmol) in dichloromethane (20 mL) was treated with SeO_2 (324 mg, 2.4 mmol) and predried *t*-BuOOH (70 % in H_2O, 1.48 mL, 10.8 mmol) over Na_2SO_4. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane (20 mL), and the organic layer was washed with saturated aq $Na_2S_2O_3$ and brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to get the crude, which was purified by column chromatography [PE:EA = 2:1 to 1:2] to give compound **2** (810 mg, 72%) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, J = 3.5 Hz, 1H, H-13), 5.60 (t, J = 8.2 Hz, 1H, H-1), 5.52 (d, J = 3.2 Hz, 1H, H-13), 4.09 (d, J = 12.9 Hz, 1H, , H-14), 4.01 (d, J = 12.9 Hz, 1H, H-14), 3.81 (t, J = 9.4 Hz, 1H, H-6), 2.87 – 2.75 (m, 2H, H-7, H-5), 2.48 – 2.29 (m, 4H, C$\underline{H}_2$, $CH_2O\underline{H}$), 2.28 – 2.04 (m, 3H, C$\underline{H}_2$), 1.65 – 1.56 (m, 1H, H-8), 1.49 (s, 3H, H-15), 1.03 (t, J = 12.4 Hz, 1H, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9(C-12), 139.5(C-11), 138.8(C-10), 126.8(C-13), 120.4(C-1), 81.4(C-6), 65.4(C-14), 63.3(C-5), 60.4(C-4), 42.7(C-7),

36.8(C-3), 25.5($\underline{C}H_2$), 24.0($\underline{C}H_2$), 23.6($\underline{C}H_2$), 18.0(C-15). HRMS (ESI) calcd for $C_{15}H_{20}NaO_4$ $[M+Na]^+$ 287.1254, found 287.1258.

*4.1.2 General procedure for the synthesis of compounds **3**, **4a**–**4x***

To a solution of compound **2** (53 mg, 0.2 mmol), EDCI (115 mg, 0.6 mmol), DMAP (1.2 mg, 0.01 mmol) and corresponded acid (0.3 mmol, 1.5 eq) in CH_2Cl_2 (2 mL) was added Et_3N (83.4 μL, 0.6 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield compound **3**, **4a**–**4x**.

*4.1.2.1 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl cinnamate (**3**)*: White solid (yield: 86%), mp 131-133 □; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 16.0 Hz, 1H, H-18), 7.54 – 7.46 (m, 2H, Ar-H), 7.45 – 7.34 (m, 3H, Ar-H), 6.41 (d, J = 16.0 Hz, 1H, H-17), 6.22 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.55 (d, J = 3.1 Hz, 1H, H-13), 4.77 (d, J = 12.5 Hz, 1H, H-14), 4.59 (d, J = 12.5 Hz, 1H, H-14), 3.85 (t, J = 9.3 Hz, 1H, H-6), 3.01 – 2.91 (m, 1H, H-7), 2.87 (d, J = 9.4 Hz, 1H, H-5), 2.49 – 2.11 (m, 6H, $C\underline{H}_2$), 1.72 – 1.64 (m, 1H, $C\underline{H}_2$), 1.54 (s, 3H, H-15), 1.10 (t, J = 12.7 Hz, 1H, $C\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.5(C-16), 145.4(C-18), 138.6(C-11), 134.8(C-10), 133.9(Ar-C), 130.6(C-1), 130.5(Ar-C), 128.8(Ar-C), 128.0(Ar-C), 120.2(C-13), 117.2(C-17), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 42.5(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{30}NO_5$ $[M+NH_4]^+$ 412.2118, found 412.2122.

*4.1.2.2 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-(trifluoromethyl)phenyl)acrylate (**4a**)*: White solid (yield: 92%), mp 146-148 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 15.8 Hz, 1H, H-18), 7.67 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.56 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.47 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.38 (d, *J* = 15.8 Hz, 1H, H-17), 6.19 (d, *J* = 3.4 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.4 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.63 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 2.91 (t, *J* = 9.0 Hz, 1H, H-5), 2.85 (d, *J* = 9.4 Hz, 1H, H-7), 2.51 – 2.09 (m, 6H, C$\underline{H}_2$), 1.69 (dd, *J* = 16.5, 8.6 Hz, 1H, C$\underline{H}_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 165.5(C-16), 140.7(C-18), 138.6(C-11), 134.7(C-10), 132.8(Ar-C), 132.1(C-1), 130.7(Ar-C), 129.7(Ar-C), 128.6 (q, *J* = 30.3 Hz, Ar-C), 127.7(Ar-C), 126.04 (q, *J* = 5.6 Hz, Ar-C), 123.8 (d, *J* = 274.1 Hz, CF_3), 121.6(C-13), 120.1(C-17), 80.9(C-6), 66.9(C-14), 63.1(C-5), 59.7(C-4), 42.5(C-7), 36.4(C-3), 25.5(C-8), 24.3(C-9), 23.7(C-2), 17.8(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –58.8 (s). HRMS (ESI) calcd for $C_{25}H_{29}F_3NO_5$ $[M+NH_4]^+$ 480.1992, found 480.1993.

*4.1.2.3 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-fluorophenyl)acrylate (**4b**)*: White solid (yield: 98%), mp 110-112 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 16.2 Hz, 1H, H-18), 7.48 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.33 (dd, *J* = 13.2, 7.0 Hz, 1H, Ar-H), 7.13 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.10 – 7.03 (m, 1H, Ar-H), 6.49 (d, *J* = 16.2 Hz, 1H, H-17), 6.19 (d, *J* = 2.0 Hz, 1H, H-13), 5.70 (t, *J* = 8.2 Hz, 1H, H-1), 5.53 (d, *J* = 2.0 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.57 (d, *J* = 12.5 Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 2.92 (t, *J* = 9.1 Hz, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.05 (m, 6H, C$\underline{H}_2$), 1.74 – 1.60 (m, 1H, C$\underline{H}_2$),

1.51 (s, 3H, H-15), 1.07 (t, *J* = 12.9 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.2(C-16), 161.2 (d, *J* = 254.1 Hz, Ar-C), 138.6(C-11), 137.9 (d, *J* = 2.3 Hz, C-18), 134.8(C-10), 131.9 (d, *J* = 8.8 Hz, Ar-C), 130.6(C-1), 129.0 (d, *J* = 2.6 Hz, Ar-C), 124.4 (d, *J* = 3.5 Hz, Ar-C), 122.0 (d, *J* = 11.5 Hz, Ar-C), 120.1(C-13), 119.8 (d, *J* = 6.7 Hz, C-17), 116.0 (d, *J* = 21.8 Hz, Ar-C), 80.9(C-6), 66.8(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.3(C-9), 23.7(C-2), 17.8(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.2 (ddd, *J* = 10.6, 7.5, 3.7 Hz). HRMS (ESI) calcd for $C_{24}H_{29}FNO_5$ $[M+NH_4]^+$ 430.2024, found 430.2019.

4.1.2.4 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-chlorophenyl)acrylate ***(4c)***: White solid (yield: 96%), mp 114-116 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 16.0 Hz, 1H, H-18), 7.57 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar-H), 7.38 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar-H), 7.28 (m, 2H, Ar-H), 6.39 (d, *J* = 16.0 Hz, 1H, H-18), 6.19 (d, *J* = 3.4 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.1 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.60 (d, *J* = 12.5 Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 3.04 – 2.89 (m, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.47 – 2.08 (m, 6H, C<u>H</u>$_2$), 1.67 (m, 1H, C<u>H</u>$_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.1(C-16), 141.3(C-18), 138.7(Ar-C), 135.0(C-11), 134.9(C-10), 132.3(C-1), 131.3(Ar-C), 130.9(Ar-C), 130.2(Ar-C), 127.6(Ar-C), 127.2(Ar-C), 120.4(C-13), 119.9(C-17), 81.0(C-6), 67.0(C-14), 63.3(C-5), 59.9(C-4), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.5(C-9), 23.8(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{24}H_{29}ClNO_5$ $[M+NH_4]^+$ 446.1729, found 446.1723.

4.1.2.5 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-bromophenyl)acrylate ***(4d)***: White solid (yield: 72%), mp 120-123 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 15.9

Hz, 1H, H-18), 7.57 (dd, *J* = 11.2, 4.5 Hz, 2H, Ar-H), 7.31 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.21 (td, *J* = 7.9, 1.4 Hz, 1H, Ar-H), 6.35 (d, *J* = 15.9 Hz, 1H, H-17), 6.20 (d, *J* = 3.4 Hz, 1H, H-13), 5.73 (t, *J* = 8.3 Hz, 1H, H-1), 5.54 (d, *J* = 3.4 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.61 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 2.98 – 2.90 (m, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.49 – 2.10 (m, 6H, C$\underline{H}_2$), 1.68 (dd, *J* = 12.8, 8.6 Hz, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 165.8(C-16), 143.6(C-18), 138.6(C-11), 134.7(C-10), 134.0(Ar-C), 133.3(C-1), 131.4(Ar-C), 130.7(Ar-C), 127.7(Ar-C), 127.6(Ar-C), 125.2(C-13), 120.2(Ar-C), 120.1(C-17), 80.9(C-6), 66.9(C-14), 63.1(C-5), 59.8(C-4), 42.6(C-7), 36.5(C-3), 25.6(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{29}BrNO_5$ $[M+NH_4]^+$ 490.1224, found 490.1214.

*4.1.2.6 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(o-tolyl)acrylate (**4e**)*: White solid (yield: 94%), mp 83-85 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 15.9 Hz, 1H, H-18), 7.52 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.29 – 7.24 (m, 1H, Ar-H), 7.20 (t, *J* = 7.0 Hz, 2H, Ar-H), 6.34 (d, *J* = 15.9 Hz, 1H, H-17), 6.22 (d, *J* = 3.5 Hz, 1H, H-13), 5.73 (t, *J* = 8.3 Hz, 1H, H-1), 5.55 (d, *J* = 3.2 Hz, 1H, H-13), 4.77 (d, *J* = 12.6 Hz, 1H, H-14), 4.60 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.00 – 2.91 (m, 1H, H-7), 2.87 (d, *J* = 9.4 Hz, 1H, H-5), 2.53 – 2.11 (m, 9H, C$\underline{H}_2$, Ar-C$\underline{H}_3$), 1.68 (dd, *J* = 13.2, 8.8 Hz, 1H, C$\underline{H}_2$), 1.54 (s, 3H, H-15), 1.10 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.5(C-16), 143.1(C-18), 138.6(C-11), 137.6(C-10), 134.9(Ar-C), 132.9(C-1), 130.7(Ar-C), 130.4(Ar-C), 130.2(Ar-C), 126.3(Ar-C), 126.2(C-13), 120.2(Ar-C), 118.2(C-17), 80.9(C-6), 66.7(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.5(C-3), 25.6(C-8), 24.4(C-9), 23.7(C-2), 19.6(Ar-$\underline{C}H_3$), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{32}NO_5$ $[M+NH_4]^+$ 426.2275, found 426.2281.

*4.1.2.7 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-methoxyphenyl)acrylate (**4f**)*: White solid (yield: 89%), mp 172-174 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 16.1 Hz, 1H, H-18), 7.46 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.35 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.00 – 6.87 (m, 2H, Ar-H), 6.50 (d, *J* = 16.1 Hz, 1H, H-17), 6.21 (d, *J* = 3.3 Hz, 1H, H-13), 5.72 (t, *J* = 8.0 Hz, 1H, H-1), 5.54 (d, *J* = 2.9 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.59 (d, *J* = 12.5 Hz, 1H, H-14), 3.96 – 3.79 (m, 4H, H-6, Ar-OC$\underline{H}_3$), 3.00 (t, *J* = 8.8 Hz, 1H, H-7), 2.89 (d, *J* = 9.4 Hz, 1H, H-5), 2.54 – 2.09 (m, 6H, C$\underline{H}_2$), 1.67 (t, *J* = 11.1 Hz, 1H, C$\underline{H}_2$), 1.54 (s, 3H, H-15), 1.11 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4(C-12), 167.1(C-16), 158.3(Ar-C), 141.0(C-11), 138.6(C-18), 135.0(C-10), 131.7(Ar-C), 130.7(C-1), 129.1(Ar-C), 122.9(Ar-C), 120.6(Ar-C), 120.3(C-13), 117.7(C-17), 111.1(Ar-C), 81.0(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 55.4(OCH_3), 42.6(C-7), 36.5(C-3), 25.8(C-8), 24.6(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{32}NO_6$ $[M+NH_4]^+$ 442.2224, found 442.2232.

*4.1.2.8 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-ethoxyphenyl)acrylate (**4g**)*: White solid (yield: 89%), mp 143-145 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 16.1 Hz, 1H, H-18), 7.48 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.33 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.97 – 6.89 (m, 2H, Ar-H), 6.52 (d, *J* = 16.1 Hz, 1H, H-17), 6.29 – 6.19 (m, 1H, H-13), 5.74 (t, *J* = 8.0 Hz, 1H, H-1), 5.55 (d, *J* = 2.9 Hz, 1H, H-13), 4.76 (d, *J* = 12.6 Hz, 1H, H-14), 4.62 (d, *J* = 12.6 Hz, 1H, H-14), 4.10 (q, *J* = 6.9 Hz, 2H, Ar-OC$\underline{H}_2$$CH_3$), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.04 – 2.95 (m, 1H, H-7), 2.89 (d, J = 9.4 Hz, 1H, H-5), 2.53 – 2.12 (m, 6H, C$\underline{H}_2$), 1.72 – 1.63 (m, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.47 (t, *J* = 6.9 Hz, 3H, Ar-OCH_2C$\underline{H}_3$), 1.12 (t, *J* = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.0(C-16), 157.5(Ar-C), 140.9(C-11), 138.5(C-18), 134.9(C-10),

131.6(Ar-C), 130.1(C-11), 128.7(Ar-C), 122.7(Ar-C), 120.3(Ar-C), 120.1(C-13), 117.3(C-17), 111.9(Ar-C), 80.8(C-6), 66.5(C-14), 63.7(C-5), 63.0(O<u>C</u>$H_2$$CH_3$), 59.8(C-4), 42.4(C-7), 36.4(C-3), 25.5(C-8), 24.3(C-9), 23.6(C-2), 17.7(C-15), 14.5(OCH_2<u>C</u>H_3). HRMS (ESI) calcd for $C_{26}H_{34}NO_6$ $[M+NH_4]^+$ 456.2381, found 456.2380.

*4.1.2.9 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-(trifluoromethyl)phenyl)acrylate (**4h**)*: White solid (yield: 69%), mp 124-126 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.60 (m, 4H, H-18, Ar-H), 7.53 (t, *J* = 7.7 Hz, 1H, Ar-H), 6.49 (d, *J* = 16.0 Hz, 1H, H-17), 6.26 (d, *J* = 3.3 Hz, 1H, H-13), 5.75 (t, *J* = 8.2 Hz, 1H, H-1), 5.57 (d, *J* = 2.9 Hz, 1H, H-13), 4.80 (d, *J* = 12.5 Hz, 1H, H-14), 4.62 (d, *J* = 12.5 Hz, 1H, H-14), 3.87 (t, *J* = 9.3 Hz, 1H, H-6), 2.93 (dd, *J* = 15.1, 6.0 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.56 – 2.14 (m, 6H, C<u>H</u>$_2$), 1.76 – 1.64 (m, 1H, C<u>H</u>$_2$), 1.56 (s, 3H, H-15), 1.13 (t, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.0(C-16), 143.7(C-18), 138.7(C-11), 134.9(C-10), 134.8(Ar-C), 131.5 (d, *J* = 32.3 Hz, Ar-C), 131.1(C-1), 130.8(Ar-C), 129.5(Ar-C), 126.9 (d, *J* = 3.7 Hz, Ar-C), 124.6 (d, *J* = 3.8 Hz, Ar-C), 123.7(d, *J* =273.30, CF_3), 120.3(C-13), 119.3(C-17), 81.0(C-6), 66.9(C-14), 63.3(C-5), 59.9(C-4), 42.7(C-7), 36.6(C-3), 25.7(C-8), 24.4(C-9), 23.8(C-2), 18.0(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.89 (s). HRMS (ESI) calcd for $C_{25}H_{29}F_3NO_5$ $[M+NH_4]^+$ 480.1992, found 480.1992.

*4.1.2.10 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-fluorophenyl)acrylate (**4i**)*: White solid (yield: 76%), mp 127-129 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16.0 Hz, 1H, H-18), 7.35 (dd, *J* = 13.8, 7.8 Hz, 1H, Ar-H), 7.27 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.19 (d, *J* = 9.5 Hz, 1H, Ar-H), 7.08 (t, *J* = 8.2 Hz, 1H, Ar-H), 6.40 (d, *J* = 16.0 Hz, 1H, H-17), 6.23 (d, *J* =

3.4 Hz, 1H, H-13), 5.73 (t, *J* = 8.2 Hz, 1H, H-1), 5.55 (d, *J* = 3.4 Hz, 1H, H-13), 4.78 (d, *J* = 12.5 Hz, 1H, H-14), 4.59 (d, *J* = 12.5 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 2.93 (dd, *J* = 14.8, 5.8 Hz, 1H, H-7), 2.87 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.11 (m, 6H, C$\underline{H}_2$), 1.70 (m, 1H, C$\underline{H}_2$), 1.54 (s, 3H, H-15), 1.11 (m, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.1(C-16), 162.9 (d, *J* = 247.0 Hz, Ar-C), 144.0 (d, *J* = 2.5 Hz, C-18), 138.7(C-11), 136.2 (d, *J* = 7.7 Hz, Ar-C), 134.8(C-10), 130.7(C-1), 130.5 (d, *J* = 8.2 Hz, Ar-C), 124.1 (d, *J* = 2.7 Hz, Ar-C), 120.2(C-13), 118.7(C-17), 117.3 (d, *J* = 21.4 Hz, Ar-C), 114.3 (d, *J* = 22.0 Hz, Ar-C), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.8(C-2), 17.9(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –112.3 (dd, *J* = 14.8, 8.9 Hz). HRMS (ESI) calcd for $C_{24}H_{29}FNO_5$ $[M+NH_4]^+$ 430.2024, found 430.2024.

4.1.2.11 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-chlorophenyl)acrylate ***(4j)***: White solid (yield: 69%), mp 114-117 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 16.0 Hz, 1H, H-18), 7.46 (s, 1H, Ar-H), 7.37-7.30 (m, 3H, Ar-H), 6.40 (d, *J* = 16.0 Hz, 1H, H-17), 6.21 (d, *J* = 3.2 Hz, 1H, H-13), 5.71 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 2.8 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.59 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 2.91 (dd, *J* = 14.7, 5.8 Hz, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.09 (m, 6H, C$\underline{H}_2$), 1.73 – 1.62 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 13.0 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.0(C-16), 143.7(C-18), 138.6(C-11), 135.8(C-10), 134.8(Ar-C), 134.7(C-1), 130.6 (Ar-C), 130.2(Ar-C), 130.1(Ar-C), 127.7(Ar-C), 126.2(Ar-C), 120.2(C-13), 118.8(C-17), 80.9(C-6), 66.8(C-14), 63.1(C-5), 59.9(C-4), 42.5(C-7), 36.5(C-3), 25.6(C-8), 24.3(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{29}ClNO_5$ $[M+NH_4]^+$ 446.1729, found 446.1723.

*4.1.2.12 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-bromophenyl)acrylate (**4k**)*: White solid (yield: 89%), mp 118-120 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, Ar-H), 7.57 (d, *J* = 16.0 Hz, 1H, H-18), 7.48 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.40 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.27 – 7.22 (m, 1H, Ar-H), 6.39 (d, *J* = 16.0 Hz, 1H, H-17), 6.21 (d, *J* = 3.4 Hz, 1H, H-13), 5.71 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.4 Hz, 1H, H-13), 4.76 (d, *J* = 12.6 Hz, 1H, H-14), 4.58 (d, *J* = 12.6 Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 2.97 – 2.88 (m, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.10 (m, 6H, C$\underline{H}_2$), 1.73 – 1.63 (m, 1H, C$\underline{H}_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.0(C-16), 143.5(C-18), 138.6(C-11), 136.0(C-10), 134.7(Ar-C), 133.1(C-1), 130.6(Ar-C), 130.5(Ar-C), 130.4(Ar-C), 126.6(Ar-C), 122.8(Ar-C), 120.1(C-13), 118.8(C-17), 80.9(C-6), 66.8(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.5(C-8), 24.3(C-9), 23.7(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{24}H_{29}BrNO_5$ $[M+NH_4]^+$ 490.1224, found 490.1218.

*4.1.2.13 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(m-tolyl)acrylate (**4l**)*: White solid (yield: 88%), mp 172-174 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H, H-18), 7.36 – 7.27 (m, 3H, Ar-H), 7.21 (d, *J* = 7.2 Hz, 1H, Ar-H), 6.42 (d, *J* = 16.0 Hz, 1H, H-17), 6.24 (d, *J* = 3.5 Hz, 1H, H-13), 5.74 (t, *J* = 8.2 Hz, 1H, H-1), 5.57 (d, *J* = 3.1 Hz, 1H, H-13), 4.78 (d, *J* = 12.5 Hz, 1H, H-14), 4.61 (d, *J* = 12.5 Hz, 1H, H-14), 3.87 (t, *J* = 9.3 Hz, 1H, H-6), 3.02 – 2.94 (m, 1H, H-7), 2.89 (d, *J* = 9.4 Hz, 1H, H-5), 2.54 – 2.13 (m, 9H, C$\underline{H}_2$, Ar-C$\underline{H}_3$), 1.75 – 1.66 (m, 1H, C$\underline{H}_2$), 1.56 (s, 3H, H-15), 1.12 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.5(C-16), 145.5(C-18), 138.6(Ar-C), 138.4(C-11), 134.8(C-10), 133.9(Ar-C), 131.2(C-1), 130.4(Ar-C), 128.7(Ar-C), 128.6(Ar-C), 125.1(Ar-C), 120.1(C-13),

117.0(C-17), 80.9(C-6), 66.7(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.4(C-9), 23.7(C-2), 21.1(Ar-$\underline{C}H_3$), 17.8(C-15). HRMS (ESI) calcd for $C_{25}H_{32}O_5$ $[M+NH_4]^+$ 426.2275，found 426.2283.

*4.1.2.14 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-methoxyphenyl)acrylate (**4m**):* White solid (yield: 92%), mp 96-98 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0 Hz, 1H, H-18), 7.29 (d, J = 7.9 Hz, 1H, Ar-H), 7.08 (d, J = 7.7 Hz, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 6.92 (dd, J = 8.2, 2.1 Hz, 1H, Ar-H), 6.39 (d, J = 16.0 Hz, 1H, H-17), 6.22 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.54 (d, J = 3.1 Hz, 1H, H-13), 4.76 (d, J = 12.5 Hz, 1H, H-14), 4.58 (d, J = 12.5 Hz, 1H, H-14), 3.85 (t, J = 9.3 Hz, 1H, H-6), 3.80 (s, 3H, Ar-OC$\underline{H}_3$), 3.00 – 2.91 (m, 1H, H-7), 2.86 (d, J = 9.4 Hz, 1H, H-7), 2.51 – 2.10 (m, 6H, C$\underline{H}_2$), 1.73 – 1.63 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, J = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.4(C-16), 159.8(Ar-C), 145.3(C-18), 138.7(C-11), 135.3(Ar-C), 134.8(C-10), 130.6(C-1), 129.8(Ar-C), 120.7(Ar-C), 120.2(C-13), 117.5(C-17), 116.3(Ar-C), 112.8(Ar-C), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 55.2(Ar-O$\underline{C}H_3$), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{32}NO_6$ $[M+NH_4]^+$ 442.2224, found 442.2229.

*4.1.2.15 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-(trifluoromethyl)phenyl)acrylate (**4n**)*: White solid (yield: 72%), mp 164-166 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 16.0 Hz, 1H, H-18), 7.63 – 7.56 (m, 4H, Ar-H), 6.47 (d, J = 16.0 Hz, 1H, H-17), 6.19 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.53 (d, J = 3.1 Hz, 1H,

H-13), 4.77 (d, *J* = 12.5 Hz, 1H, H-14), 4.60 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 2.93 (dd, *J* = 14.9, 5.9 Hz, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.09 (m, 6H, C$\underline{H}_2$), 1.73 – 1.65 (m, 1H, C$\underline{H}_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 165.9(C-16), 143.4(C-18), 138.7(C-11), 137.4(Ar-C), 134.6(C-10), 131.6 (q, *J* = 32.6 Hz, Ar-C), 130.7(C-1), 128.1(Ar-C), 125.72 (q, *J* = 3.7 Hz, Ar-C), 123.6 (d, *J* = 272.3 Hz, $\underline{C}F_3$), 120.1(C-13), 119.9(C-17), 80.9(C-6), 66.9(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.5(C-8), 24.3(C-9), 23.7(C-2), 17.8(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.9 (s). HRMS (ESI) calcd for $C_{25}H_{29}F_3NO_5$ $[M+NH_4]^+$ 480.1992, found 480.2000.

*4.1.2.16 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-fluorophenyl)acrylate (**4o**)*: White solid (yield: 93%), mp 78-80 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 16.0 Hz, 1H, H-18), 7.55 – 7.43 (m, 2H, Ar-H), 7.06 (t, *J* = 8.6 Hz, 2H, Ar-H), 6.32 (d, *J* = 16.0 Hz, 1H, H-17), 6.21 (d, *J* = 3.5 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.5 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.58 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 3.01 – 2.90 (m, 1H, H-7), 2.87 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.10 (m, 6H, C$\underline{H}_2$), 1.73 – 1.64 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.10 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.4(C-16), 163.9 (d, *J* = 251.9 Hz, Ar-C), 144.1(C-18), 138.7(C-11), 134.8(C-10), 130.6(C-1), 130.3 (d, *J* = 3.2 Hz, Ar-C), 129.9 (d, *J* = 8.6 Hz, Ar-C), 120.2(C-13), 117.0(C-17), 116.0 (d, *J* = 22.0 Hz, Ar-C), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –109.0 (s). HRMS (ESI) calcd for $C_{24}H_{29}FNO_5$ $[M+NH_4]^+$ 430.2024, found 430.2026.

*4.1.2.17 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-chlorophenyl)acrylate (**4p**):* White solid (yield: 90%), mp 148-150 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 16.0 Hz, 1H, H-18), 7.42 (d, J = 8.5 Hz, 2H, Ar-H), 7.34 (d, J = 8.5 Hz, 2H, Ar-H), 6.37 (d, J = 16.0 Hz, 1H, H-17), 6.21 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.54 (d, J = 3.2 Hz, 1H, H-13), 4.76 (d, J = 12.5 Hz, 1H, H-14), 4.58 (d, J = 12.5 Hz, 1H, H-14), 3.85 (t, J = 9.3 Hz, 1H, H-6), 3.00 – 2.89 (m, 1H, H-7), 2.86 (d, J = 9.4 Hz, 1H, H-5), 2.52 – 2.10 (m, 6H, C$\underline{H}_2$), 1.72 – 1.63 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, J = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.2(C-16), 143.9(C-18), 138.7(C-11), 136.3(C-10), 134.8(Ar-C), 132.5(Ar-C), 130.7(C-1), 129.2(Ar-C), 129.1(Ar-C), 120.2(C-13), 117.9(C-17), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{29}ClNO_5$ $[M+NH_4]^+$ 446.1729, found 446.1732.

*4.1.2.18 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-bromophenyl)acrylate(**4q**)*: White solid (yield: 86%), mp 177-179 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 16.0 Hz, 1H, H-18), 7.49 (d, J = 8.4 Hz, 2H, Ar-H), 7.35 (d, J = 8.4 Hz, 2H, Ar-H), 6.39 (d, J = 16.0 Hz, 1H, H-17), 6.21 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.53 (d, J = 3.1 Hz, 1H, H-13), 4.76 (d, J = 12.5 Hz, 1H, H-14), 4.58 (d, J = 12.5 Hz, 1H, H-14), 3.85 (t, J = 9.3 Hz, 1H, H-6), 2.93 (m, 1H, H-7), 2.86 (d, J = 9.4 Hz, 1H, H-5), 2.51 – 2.11 (m, 6H, C$\underline{H}_2$), 1.73 – 1.63 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, J = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3(C-12), 166.2(C-16), 144.0(C-18), 138.6(C-11), 134.7(C-10), 132.9(Ar-C), 132.1(Ar-C), 130.7(C-1), 129.4(Ar-C), 124.7(Ar-C), 120.2(C-13), 118.0(C-17),

80.9(C-6), 66.8(C-14), 63.1(C-5), 59.9(C-4), 42.5(C-7), 36.5(C-3), 25.6(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{29}BrNO_5$ $[M+NH_4]^+$ 490.1224, found 490.1221.

*4.1.2.19 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(p-tolyl)acrylate (**4r**)*: White solid (yield: 62%), mp 153-155 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 16.0 Hz, 1H, H-18), 7.40 (d, J = 8.0 Hz, 2H, Ar-H), 7.19 (d, J = 7.9 Hz, 2H, Ar-H), 6.36 (d, J = 16.0 Hz, 1H, H-17), 6.23 (d, J = 3.5 Hz, 1H, H-13), 5.73 (t, J = 8.2 Hz, 1H, H-1), 5.55 (d, J = 3.1 Hz, 1H, H-13), 4.77 (d, J = 12.5 Hz, 1H, H-14), 4.59 (d, J = 12.5 Hz, 1H, H-14), 3.86 (t, J = 9.3 Hz, 1H, H-6), 3.01 – 2.92 (m, 1H, H-7), 2.88 (d, J = 9.4 Hz, 1H, H-5), 2.52 – 2.12 (m, 9H, C<u>H</u>$_2$, Ar-C<u>H</u>$_3$), 1.68 (dd, J = 12.8, 8.5 Hz, 1H, C<u>H</u>$_2$), 1.55 (s, 3H, H-15), 1.11 (t, J = 12.7 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.7(C-16), 145.5(C-18), 141.0(Ar-C), 138.7(C-13), 135.0(C-10), 131.3(Ar-C), 130.6(C-1), 129.6(Ar-C), 128.1(Ar-C), 120.3(C-13), 116.1(C-17), 81.0(C-6), 66.7(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.8(C-8), 24.5(C-9), 23.8(C-2), 21.4(Ar-<u>C</u>H$_3$), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{32}NO_5$ $[M+NH_4]^+$ 426.2275, found 426.2281.

*4.1.2.20 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-isopropylphenyl)acrylate (**4s**)*: White solid (yield: 71%), mp 147-149 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 16.0 Hz, 1H, H-18), 7.43 (d, J = 8.1 Hz, 2H, Ar-H), 7.23 (d, J = 8.1 Hz, 2H, Ar-H), 6.36 (d, J = 16.0 Hz, 1H, H-17), 6.22 (d, J = 3.5 Hz, 1H, H-13), 5.72 (t, J = 8.2 Hz, 1H, H-1), 5.55 (d, J = 3.1 Hz, 1H, H-13), 4.76 (d, J = 12.5 Hz, 1H, H-14), 4.58 (d, J = 12.5 Hz, 1H, H-14), 3.86 (t, J = 9.3 Hz, 1H, H-6), 2.93 (m, 3H, H-5, -7, Ar-C<u>H</u>), 2.51 – 2.10 (m, 6H, C<u>H</u>$_2$), 1.68 (dd, J = 12.9, 8.8 Hz, 1H, C<u>H</u>$_2$), 1.54 (s, 3H, H-15), 1.23 (d, J = 6.9 Hz, 6H,Ar-CH(C<u>H</u>$_3$)$_2$),

1.10 (t, *J* = 13.2 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.7(C-16), 151.8(Ar-C), 145.4(C-18), 138.6(C-11), 134.9(C-10), 131.6(Ar-C), 130.5(C-1), 128.1(Ar-C), 126.9(Ar-C), 120.2(C-13), 116.2(C-17), 80.9(C-6), 66.7(C-14), 63.1(C-5), 59.9(C-4), 42.5(C-7), 36.5(C-3), 33.9(Ar-<u>C</u>HCH3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 23.6(Ar-CH<u>C</u>H3), 17.9(C-15). HRMS (ESI) calcd for $C_{27}H_{36}NO_5$ $[M+NH_4]^+$ 454.2588, found 454.2594.

*4.1.2.21 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-methoxyphenyl)acrylate (**4t**)*: White solid (yield: 77%), mp 185-188 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 15.9 Hz, 1H, H-18), 7.45 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.27 (d, *J* = 15.9 Hz, 1H, H-17), 6.23 (d, *J* = 3.5 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.55 (d, *J* = 3.1 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.57 (d, *J* = 12.5 Hz, 1H, H-14), 3.89 – 3.83 (m, 1H, H-6), 3.82 (s, 3H, Ar-OC<u>H</u>$_3$), 2.97 (dd, *J* = 14.8, 5.8 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.12 (m, 6H, C<u>H</u>$_2$), 1.67 (dd, *J* = 12.7, 8.6 Hz, 1H, C<u>H</u>$_2$), 1.54 (s, 3H, H-15), 1.10 (t, *J* = 12.7 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.9(C-16), 161.5(Ar-C), 145.1(C-18), 138.7(C-11), 135.0(C-10), 130.5(C-1), 129.7(Ar-C), 126.7(Ar-C), 120.3(C-13), 114.6(C-17), 114.3(Ar-C), 81.0(C-6), 66.7(C-14), 63.2(C-5), 59.9(C-4), 55.3(Ar-O<u>C</u>H$_3$), 42.6(C-7), 36.5(C-3), 25.8(C-8), 24.5(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{32}NO_6$ $[M+NH_4]^+$ 442.2224, found 442.2230.

*4.1.2.22 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-ethoxyphenyl)acrylate (**4u**)*: White solid (yield: 90%), mp 142-145 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 15.9 Hz, 1H, H-18), 7.42 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.86 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.25 (d, *J* = 15.9 Hz, 1H, H-17), 6.21 (d, *J* = 3.4 Hz, 1H, H-13), 5.70 (t, J = 8.1 Hz, 1H, H-1), 5.54 (d, *J* = 3.2 Hz,

1H, H-13), 4.74 (d, *J* = 12.5 Hz, 1H, H-14), 4.56 (d, *J* = 12.5 Hz, 1H, H-14), 4.03 (q, *J* = 6.9 Hz, 2H,OC$\underline{H}_2$CH$_3$), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 2.95 (t, *J* = 8.9 Hz, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.49 – 2.10 (m, 6H, C$\underline{H}_2$), 1.66 (t, *J* = 10.7 Hz, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.39 (t, *J* = 7.0 Hz, 3H,OCH$_2$C$\underline{H}_3$), 1.09 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 169.3(C-12), 166.8(C-16), 160.9(Ar-C), 145.1(C-18), 138.6(C-11), 135.0(C-10), 130.3(C-1), 129.7(Ar-C), 126.5(Ar-C), 120.2(C-13), 114.7(C-17), 114.4(Ar-C), 80.9(C-6), 66.6(C-14), 63.5(C-5), 63.1(Ar-$\underline{C}$H$_2$CH$_3$), 59.8(C-4), 42.5(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.8(C-5), 14.6(Ar-CH$_2\underline{C}$H$_3$). HRMS (ESI) calcd for C$_{26}$H$_{34}$NO$_6$ [M+NH$_4$]$^+$ 456.2381, found 456.2390.

*4.1.2.23 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-acetoxyphenyl)acrylate(**4v**)*: White solid (yield: 78%), mp 81-83 □. ^{1}H NMR (400 MHz, CDCl$_3$) *δ* 7.63 (d, *J* = 16.0 Hz, 1H, H-18), 7.50 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.10 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.35 (d, *J* = 16.0 Hz, 1H, H-17), 6.20 (d, *J* = 3.4 Hz, 1H, H-13), 5.70 (t, *J* = 8.2 Hz, 1H, H-1), 5.53 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.57 (d, *J* = 12.5 Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 2.92 (dd, *J* = 14.8, 5.8 Hz, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.09 (m, 9H, C$\underline{H}_2$, ArOCOC$\underline{H}_3$), 1.71 – 1.62 (m, 1H, C$\underline{H}_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 169.3(C-12), 169.0(Ar-O$\underline{C}$OCH$_3$), 166.3(C-16), 152.1(Ar-C), 144.2(C-18), 138.6(C-11), 134.8(C-10), 131.6(Ar-C), 130.5(C-1), 129.1(Ar-C), 122.1(Ar-C), 120.2(C-13), 117.4(C-17), 80.9(C-6), 66.7(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.3(C-9), 23.7(C-2), 21.0(Ar-OCO$\underline{C}$H$_3$), 17.8(C-15). HRMS (ESI) calcd for C$_{26}$H$_{32}$NO$_7$ [M+NH$_4$]$^+$ 470.2173, found 470.2171.

*4.1.2.24 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-nitrophenyl)acrylate (**4w**):* White solid (yield: 53%), mp 216-218 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.7 Hz, 2H, Ar-H), 7.71 (d, J = 16.1 Hz, 1H, H-18), 7.66 (d, J = 8.7 Hz, 2H, Ar-H), 6.54 (d, J = 16.0 Hz, 1H, H-17), 6.24 (d, J = 3.5 Hz, 1H, H-13), 5.75 (t, J = 8.2 Hz, 1H, H-1), 5.56 (d, J = 3.1 Hz, 1H, H-13), 4.80 (d, J = 12.5 Hz, 1H, H-14), 4.63 (d, J = 12.5 Hz, 1H, H-14), 3.87 (t, J = 9.3 Hz, 1H, H-6), 3.00 – 2.91 (m, 1H, H-7), 2.88 (d, J = 9.4 Hz, 1H, H-5), 2.35 (m, 6H, C$\underline{H}_2$), 1.76 – 1.66 (m, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.12 (t, J = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 165.6(C-16), 148.6(Ar-C), 142.5(C-18), 140.1, 138.7(C-11), 134.6(C-10), 131.1(C-1), 128.7(Ar-C), 124.2(Ar-C), 121.6(C-13), 120.2(C-17), 81.0(C-6), 67.1(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{29}N2O_7$ $[M+NH_4]^+$ 457.1969, found 457.1970.

*4.1.2.25 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-cyanophenyl)acrylate (**4x**)*: White solid (yield: 82%), mp 217-219 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.57 (m, 5H, H-18, Ar-H), 6.50 (d, J = 16.0 Hz, 1H, H-17), 6.26 (d, J = 3.5 Hz, 1H, H-13), 5.76 (t, J = 8.1 Hz, 1H, H-1), 5.56 (d, J = 3.1 Hz, 1H, H-13), 4.80 (d, J = 12.5 Hz, 1H, H-14), 4.62 (d, J = 12.5 Hz, 1H, H-14), 3.87 (t, J = 9.3 Hz, 1H, H-6), 3.01 – 2.92 (m, 1H, H-7), 2.88 (d, J = 9.4 Hz, 1H, H-5), 2.56 – 2.14 (m, 6H, C$\underline{H}_2$), 1.77 – 1.67 (m, 1H, C$\underline{H}_2$), 1.56 (s, 3H, H-15), 1.13 (t, J = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4(C-12), 165.9(C-16), 143.3(C-18), 138.9(Ar-C), 138.5(C-11), 134.8(C-10), 132.9(Ar-C), 131.3(C-1), 128.6(Ar-C), 121.1(Ar-C), 120.4(C-13), 118.4(C-17), 113.8(Ar-$\underline{C}$N), 81.1(C-6), 67.3(C-14), 63.4(C-5), 60.1(C-4), 42.8(C-7), 36.7(C-3),

25.9(C-8), 24.7(C-9), 24.0(C-2), 18.1(C-15). HRMS (ESI) calcd for $C_{25}H_{29}N2O_5$ $[M+NH_4]^+$ 437.2071, found 437.2074.

*4.1.3 General procedure for the synthesis of compounds **5a** and **5b**.*

To a solution of compound **2** (264.3 mg, 1.0 mmol, 1 eq), PPh_3 (393.5 mg, 1.5 mmol) and corresponding acid (1.5 mmol, 1.5 eq) in dry THF (10 mL) were added DIAD (297 μL, 1.5 mmol, 1.5 eq) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 8 h. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA=2:1–1:2] to give compounds **5a** and **5b** as a white solid.

*4.1.3.1 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxyphenyl)acrylate (**5a**)*: White solid (yield: 76%), mp 171-173 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H, H-18), 7.38 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.13-6.99 (m, 1H, Ar-O<u>H</u>), 6.87 (d, *J* = 8.4 Hz, 2H, Ar-H), , 6.25 (d, *J* = 15.9, 3.4 Hz, 2H, H-18, H-13) 5.72 (t, *J* = 7.9 Hz, 1H, H-1), 5.57 (d, *J* = 3.3 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.59 (d, *J* = 12.5 Hz, 1H, H-14), 3.89 (t, *J* = 9.3 Hz, 1H, H-6), 2.98 (t, *J* = 9.1 Hz, 1H, H-7), 2.91 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.11 (m, 6H, C<u>H</u>$_2$), 1.73 – 1.64 (m, 1H, C<u>H</u>$_2$), 1.55 (s, 3H, H-15), 1.12 (t, *J* = 12.6 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9(C-12), 167.3(C-16), 158.6(Ar-C), 145.7(C-18), 138.5(C-11), 134.9(C-10), 130.6(Ar-C), 130.1(C-1), 126.3(Ar-C), 120.8(C-13), 116.0(Ar-C), 114.1(C-17), 81.2(C-6), 66.8(C-14), 63.3(C-5), 60.3(C-4), 42.6(C-7), 36.5(C-3),

25.8(C-8), 24.5(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{24}H_{30}NO_6$ $[M+NH_4]^+$ 428.2068, found 428.2067.

*4.1.3.2 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (**5b**)*: White solid (yield: 55%), mp 182-184 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H, H-18), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H, Ar-H), 7.00 (d, *J* = 1.8 Hz, 1H, Ar-H), 6.92 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.25 (d, *J* = 15.9, 3.5 Hz, 2H, H-17, H-13), 5.88 (s, 1H, Ar-OH), 5.75 (t, *J* = 8.3 Hz, 1H, H-1), 5.56 (d, *J* = 3.2 Hz, 1H, H-13), 4.78 (d, *J* = 12.4 Hz, 1H, H-14), 4.60 (d, *J* = 12.4 Hz, 1H, H-14), 3.94 (s, 3H, Ar-OC$\underline{H}_3$), 3.88 (t, *J* = 9.3 Hz, 1H, H-6), 3.09 – 2.98 (m, 1H, H-7), 2.91 (d, *J* = 9.4 Hz, 1H, H-5), 2.55 – 2.14 (m, 6H, C$\underline{H}_2$), 1.70 (dd, *J* = 16.9, 9.1 Hz, 1H, C$\underline{H}_2$), 1.56 (s, 3H, H-15), 1.14 (t, *J* = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4(C-12), 166.8(C-16), 148.2(Ar-C), 146.8(Ar-C), 145.6(C-18), 138.8(C-11), 135.0(C-10), 130.8(C-1), 126.6(Ar-C), 123.2(Ar-C), 120.3(C-13), 114.7(C-17), 114.6(Ar-C), 109.2(Ar-C), 81.0(C-6), 66.9(C-14), 63.3(C-5), 60.0(C-4), 55.9(Ar-O$\underline{C}H_3$), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.7(C-9), 23.8(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{25}H_{29}O_7$ $[M+H]^+$ 441.1908, found 441.1910.

*4.1.4 General procedure for the synthesis of compounds **6c–6e.***

To a stirred solution of corresponding acid (0.6 mmol, 1.2 eq) in dry CH_2Cl_2 (6 mL) at 0 °C was added oxalyl chloride (51 μL, 0.6 mmol, 1.2 eq) and then *N*,*N*-dimethylformamide (one drop). The mixture was stirred for 1.5 h at room temperature. The solvent was removed under vacuum at 25 °C to give the acid chloride. The acid chloride was dissolved in dry CH_2Cl_2 (6 mL), then compound **2** (132 mg, 0.5 mmol, 1 eq) and TEA (83 μL, 0.6 mmol, 1.2 eq) was added, the

mixture was stirred for 2h at room temperature. The solvent was removed under vacuum to give an oily crude product, which was purified on a silica gel column [PE: EA = 2:1 to 1:1] to give compounds **6c**–**6e** as a white solid.

*4.1.4.1 ((1aR,7aS,10aS,10bS,E)-1a-methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(pyridin-2-yl)acrylate (**6c**)*: colorless oil (yield: 77%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 3.7 Hz, 1H, Ar-H), 7.74 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.69 (d, *J* = 15.7 Hz, 1H, H-18), 7.42 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.32 – 7.26 (m, 1H, Ar-H), 6.93 (d, *J* = 15.7 Hz, 1H, H-17), 6.25 (d, *J* = 2.9 Hz, 1H, H-13), 5.74 (t, *J* = 7.9 Hz, 1H, H-1), 5.56 (d, *J* = 2.3 Hz, 1H, H-13), 4.78 (d, *J* = 12.6 Hz, 1H, H-14), 4.63 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 2.95 (d, *J* = 9.0 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.54 – 2.11 (m, 6H, C$\underline{H}_2$), 1.69 (t, *J* = 10.3 Hz, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.17 – 1.07 (m, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6(C-12), 166.6(C-16), 152.8(Ar-C), 150.4(Ar-C), 144.4(C-18), 138.8(C-11), 137.1(Ar-C), 135.1(C-10), 130.8(C-1), 124.8(Ar-C), 124.7(Ar-C), 121.8(C-13), 120.7(C-17), 81.2(C-6), 67.1(C-14), 63.5(C-5), 60.2(C-4), 42.9(C-7), 36.8(C-3), 26.0(C-8), 24.6(C-9), 24.1(C-2), 18.2(C-15). HRMS (ESI) calcd for $C_{23}H_{26}NO_5$ $[M+H]^+$396.1805, found 396.1800.

*4.1.4.2 ((1aR,7aS,10aS,10bS,E)-1a-methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(pyridin-3-yl)acrylate (**6d**):* colorless oil (yield: 71%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H, Ar-H), 8.62 (s, 1H, Ar-H), 7.83 (d, *J* = 6.6 Hz, 1H, Ar-H), 7.69 (d, *J* = 15.7 Hz, 1H, H-18), 7.35 (s, 1H, Ar-H), 6.50 (d, *J* = 15.9 Hz, 1H, H-17), 6.27 (s, 1H, H-13), 5.76 (t, *J* = 8.3 Hz, 1H, H-1), 5.57 (s, 1H, H-13), 4.81 (d, *J* = 12.2 Hz, 1H, H-14), 4.62 (d, *J* = 12.2 Hz, 1H, H-14), 3.88 (t, *J* = 9.1 Hz, 1H, H-6), 2.99 – 2.92 (m, 1H, H-7), 2.89 (d, *J* = 9.6 Hz, 1H, H-5), 2.53 – 2.14 (m, 6H, C$\underline{H}_2$), 1.69 (d, *J* =

12.4 Hz, 1H, C<u>H</u>$_2$), 1.56 (s, 3H, H-15), 1.13 (t, *J* = 13.2 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.5(C-12), 166.1(C-16), 151.3(Ar-C), 149.8(Ar-C), 141.9(C-18), 138.7(C-11), 134.8(C-10), 134.3(Ar-C), 131.0(C-1), 130.1(Ar-C), 123.8(Ar-C), 120.4(C-13), 119.5(C-17), 81.0(C-6), 67.0(C-14), 63.3(C-5), 59.9(C-4), 42.7(C-7), 36.6(C-3), 25.7(C-8), 24.4(C-9), 23.9(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{23}H_{26}NO_5$ [M+H] $^+$396.1805, found 396.1802.

*4.1.4.3 ((1aR,7aS,10aS,10bS,E)-1a-methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(pyridin-4-yl)acrylate (**6e**):* colorless oil (yield: 67%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.63 (d, *J* = 5.0 Hz, 2H, Ar-H), 7.58 (d, *J* = 16.1 Hz, 1H, H-18), 7.34 (d, *J* = 5.6 Hz, 2H, Ar-H), 6.57 (d, *J* = 16.1, 1H, H-17), 6.22 (d, *J* = 3.4 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.0 Hz, 1H, H-13), 4.78 (d, *J* = 12.5 Hz, 1H, H-14), 4.60 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 2.91 (dd, *J* = 15.1, 6.0 Hz, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.47 – 2.13 (m, 6H, C<u>H</u>$_2$), 1.73 – 1.64 (m, 1H, C<u>H</u>$_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 12.9 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.3(C-12), 165.6(C-16), 150.4(Ar-C), 142.4(Ar-C), 141.3(C-18), 138.6(C-11), 134.5(C-10), 131.0(C-1), 122.1(Ar-C), 121.8(C-13), 120.3(C-17), 80.9(C-6), 67.1(C-14), 63.2(C-5), 59.9(C-4), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.3(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{23}H_{26}NO_5$ [M+H] $^+$396.1805, found 396.1802.

*4.1.5 General procedure for the synthesis of compounds **6a-6b**, **6f–6g** and **7a–7m***. To a solution of compound **2** (53 mg, 0.2 mmol, 1 eq), EDCI (115 mg, 0.6 mmol, 2 eq), DMAP (1.2 mg, 0.01 mmol, 0.05 eq) and corresponded acid (0.3 mmol, 1.5 eq) in CH_2Cl_2 (2 mL) was added Et_3N (83.4 μL, 0.6 mmol, 2 eq) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and

concentrated to give an oily crude product, which was purified on a silica gel column to yield compound ***6a-6b***, ***6f–6g*** and **7a–7 m**.

*4.1.5.1 ((1aR,7aS,10aS,10bS,E)-1a-methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(furan-2-yl)acrylate (**6a**)*: colorless oil (yield: 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H, Ar-H), 7.42 (d, *J* = 15.7 Hz, 1H, H-18), 6.62 (d, *J* = 3.3 Hz, 1H, Ar-H), 6.47 (dd, *J* = 3.2, 1.7 Hz, 1H, Ar-H), 6.28 (d, *J* = 15.7 Hz, 1H, H-18), 6.24 (d, *J* = 3.4 Hz, 1H, H-13), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.55 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.6 Hz, 1H, H-14), 4.58 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.01 – 2.91 (m, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.47 – 2.13 (m, 6H, C$\underline{H}_2$), 1.72 – 1.63 (m, 1H, C$\underline{H}_2$), 1.54 (s, 3H, H-15), 1.11 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.6(C-16), 150.5(Ar-C), 145.0(Ar-C), 138.6(C-11), 134.9(C-10), 131.6(C-1), 130.5(C-18), 120.3(C-13), 115.3(C-17), 114.8(Ar-C), 112.3(Ar-C), 80.9(C-6), 66.7(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{22}H_{28}NO_6$ $[M+NH_4]^+$402.1911, found 402.1910.

*4.1.5.2 ((1aR,7aS,10aS,10bS,E)-1a-methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(thiophen-2-yl)acrylate (**6b**)*: colorless oil (yield: 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 15.7 Hz, 1H, H-18), 7.37 (d, *J* = 5.0 Hz, 1H, Ar-H), 7.24 (d, *J* = 3.4 Hz, 1H, Ar-H), 7.03 (dd, *J* = 4.9, 3.8 Hz, 1H, Ar-H), 6.22 (d, *J* = 3.5 Hz, 1H, H-13), 6.18 (d, *J* = 15.7 Hz, 1H, H-17), 5.70 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.56 (d, *J* = 12.5 Hz, 1H, H-14), 3.85 (t, *J* = 9.3 Hz, 1H, H-6), 3.01 – 2.89 (m, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.53 – 2.10 (m, 6H, C$\underline{H}_2$), 1.73 – 1.62 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.3(C-16), 139.1(Ar-C), 138.6(C-18), 137.8(C-11),

134.9(C-10), 131.3(C-1), 130.6(Ar-C), 128.8(Ar-C), 128.1(Ar-C), 120.2(C-13), 115.9(C-17), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{22}H_{28}NO_5S$ $[M+NH_4]^+$418.1683, found 418.1678.

*4.1.5.3 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(naphthalen-2-yl)acrylate (**6f**)*: White solid (yield: 93%), mp 185-187 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.81 (m, 5H, H-18, Ar-H), 7.65 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.53 (dd, *J* = 8.9, 4.5 Hz, 2H, Ar-H), 6.53 (d, *J* = 16.0 Hz, 1H, H-17), 6.27 (d, *J* = 3.3 Hz, 1H, H-13), 5.77 (t, *J* = 8.2 Hz, 1H, H-1), 5.58 (d, *J* = 3.3 Hz, 1H, H-13), 4.81 (d, *J* = 12.5 Hz, 1H, H-14), 4.63 (d, *J* = 12.5 Hz, 1H, H-14), 3.88 (t, *J* = 9.3 Hz, 1H, H-6), 2.99 (t, *J* = 9.1 Hz, 1H, H-7), 2.91 (d, *J* = 9.4 Hz, 1H, H-5), 2.55 – 2.15 (m, 6H, C$\underline{H}_2$), 1.70 (m, 1H, C$\underline{H}_2$), 1.57 (s, 3H, H-15), 1.14 (t, *J* = 12.9 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4(C-12), 166.7(C-16), 145.6(C-18), 138.7(C-11), 135.0(C-10), 134.3(Ar-C), 133.2(Ar-C), 131.6(Ar-C), 130.8(Ar-C), 130.2(C-1), 128.8(Ar-C), 128.6(Ar-C), 127.8(Ar-C), 127.4(Ar-C), 126.8(Ar-C), 123.3(Ar-C), 120.4(C-13), 117.4(C-17), 81.0(C-6), 66.9(C-14), 63.3(C-5), 59.9(C-4), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.6(C-9), 23.9(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{28}H_{32}NO_5$ $[M+NH_4]^+$ 462.2275, found 462.2283.

*4.1.5.4 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(benzo[d][1,3]dioxol-5-yl)acrylate (**6g**)*: White solid (yield: 94%), mp 219-221 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 15.9 Hz, 1H, H-18), 6.98 (d, *J* = 9.1 Hz, 2H, Ar-H), 6.80 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.23 (d, *J* = 15.9, 3.5 Hz, 2H, H-17, H-13), 6.00 (s, 2H, OC$\underline{H}_2$O), 5.72 (t, *J* = 8.2 Hz, 1H, H-1), 5.55 (d, *J* = 3.1 Hz, 1H, H-13), 4.76 (d, *J* = 12.6 Hz, 1H, H-14), 4.57 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.00 – 2.90 (m, 1H, H-7), 2.87 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.12 (m, 6H,

C<u>H</u>$_2$), 1.70-1.65 (m, 1H, C<u>H</u>$_2$), 1.54 (s, 3H, H-15), 1.11 (t, *J* = 12.7 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.7(C-16), 149.8(Ar-C), 148.3(Ar-C), 145.2(C-18), 138.7(C-11), 135.0(C-10), 130.5(C-1), 128.4(Ar-C), 124.6(Ar-C), 120.3(C-13), 115.1(C-17), 108.5(Ar-C), 106.4(Ar-C), 101.6(Ar-O<u>C</u>H$_2$O), 81.0(C-6), 66.7(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.4(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{25}H_{30}NO_7$ $[M+NH_4]^+$ 456.2017, found 456.2022.

*4.1.5.5 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,3-dimethoxyphenyl)acrylate (**7a**)*: White solid (yield: 89%), mp 72-75 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 16.2 Hz, 1H, H-18), 7.13 – 7.07 (m, 1H, Ar-H), 7.03 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.97 – 6.89 (m, 1H, Ar-H), 6.44 (d, *J* = 16.2 Hz, 1H, H-17), 6.20 (d, *J* = 3.4 Hz, 1H, H-13), 5.71 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.58 (d, *J* = 12.6 Hz, 1H, H-14), 3.87 – 3.81 (m, 7H, H-6, Ar-OC<u>H</u>$_3$), 3.00 – 2.89 (m, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.09 (m, 6H, C<u>H</u>$_2$), 1.71 – 1.62 (m, 1H, C<u>H</u>$_2$), 1.52 (s, 3H), 1.08 (t, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5(C-12), 166.8(C-16), 153.1(Ar-C), 148.5(Ar-C), 140.3(Ar-C), 138.8(C-11), 135.1(C-18), 130.6 (C-10), 128.2 (C-1), 124.3(Ar-C), 120.4(C-13), 119.2(Ar-C), 118.6(C-17), 114.2(Ar-C), 81.1(C-6), 66.8(C-14), 63.3(C-5), 61.3(Ar-O<u>C</u>H$_3$), 60.0(C-4), 55.9(Ar-O<u>C</u>H$_3$), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.5(C-9), 23.9(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ $[M+NH_4]^+$ 472.2330, found 472.2332.

*4.1.5.6 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,4-dimethoxyphenyl)acrylate(**7b**)*: White solid (yield: 94%), mp 71-73 □. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.90 (d, *J* = 16.1 Hz, 1H, H-18), 7.41 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.50 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar-H), 6.45 (d, *J* = 2.3 Hz, 1H, Ar-H), 6.41 (d, *J* = 16.1 Hz, 1H, H-17), 6.23 (d, *J* = 3.5 Hz, 1H, H-13), 5.74 (t, *J* = 8.2 Hz, 1H, H-1), 5.55 (d, *J* = 3.2 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.59 (d, *J* = 12.5 Hz, 1H, H-14), 3.91 – 3.81 (m, 7H, H-6, Ar-OC$\underline{H}_3$), 3.10 – 3.00 (m, 1H, H-7), 2.92 (d, *J* = 9.4 Hz, 1H, H-5), 2.29 (dd, *J* = 87.9, 29.8 Hz, 6H, C$\underline{H}_2$), 1.68 (t, *J* = 11.2 Hz, 1H, C$\underline{H}_2$), 1.56 (s, 3H, H-15), 1.14 (t, *J* = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, CDCl3) δ 169.4(C-12), 167.6(C-16), 162.9(Ar-C), 160.0(Ar-C), 141.0(C-11), 138.7(C-18), 135.3(C-10), 130.8(C-1), 130.7(Ar-C), 120.4(C-13), 116.2(C-17), 115.0(Ar-C), 105.3(Ar-C), 98.3(Ar-C), 81.0(C-6), 66.8(C-14), 63.3(C-5), 60.0(C-4), 55.4(Ar-O$\underline{C}H_3$), 53.4(Ar-O$\underline{C}H_3$), 42.7(C-7), 36.6(C-3), 26.0(C-8), 24.8(C-9), 23.8(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{26}H_{31}O_7$ $[M+H]^+$ 455.2064, found 455.2061.

*4.1.5.7 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,5-dimethoxyphenyl)acrylate (**7c**)*: White solid (yield: 83%), mp 139-141 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 16.1 Hz, 1H, H-18), 6.99 (d, *J* = 3.0 Hz, 1H, Ar-H), 6.90 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar-H), 6.83 (d, *J* = 9.0 Hz, 1H, Ar-H), 6.46 (d, *J* = 16.1 Hz, 1H, H-17), 6.20 (d, *J* = 3.4 Hz, 1H, H-13), 5.72 (t, *J* = 8.1 Hz, 1H, H-1), 5.53 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.5 Hz, 1H, H-14), 4.58 (d, *J* = 12.5 Hz, 1H, H-14), 3.86 (d, *J* = 9.3 Hz, 1H, H-6), 3.82 (s, 3H, Ar-OC$\underline{H}_3$), 3.76 (s, 3H, Ar-OC$\underline{H}_3$), 3.00 (dd, *J* = 14.8, 5.8 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.52 – 2.11 (m, 6H, C$\underline{H}_2$), 1.66 (dd, *J* = 13.1, 9.1 Hz, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.10 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.9(C-16), 153.3(Ar-C), 152.8(Ar-C), 140.7(C-11), 138.6(C-18), 135.0(C-10), 130.7(C-1), 123.3(C-13), 120.2(C-17), 117.9(Ar-C), 117.4(Ar-C), 113.2(Ar-C), 112.3(Ar-C), 80.9(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 55.9(Ar-

O<u>C</u>H$_3$), 55.7(Ar-O<u>C</u>H$_3$), 42.6(C-7), 36.5(C-3), 25.8(C-8), 24.6(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ $[M+NH_4]^+$ 472.2330, found 472.2328.

*4.1.5.8 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,6-dimethoxyphenyl)acrylate (**7d**)*: White solid (yield: 84%), mp 154-157 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 16.3 Hz, 1H, H-18), 7.30 – 7.22 (m, 1H, overlarp with $CHCl_3$, H-4'), 6.83 (d, J = 16.3 Hz, 1H, H-17), 6.54 (d, J = 8.4 Hz, 2H, H-3', H-5'), 6.19 (d, J = 3.5 Hz, 1H, H-13), 5.73 (t, J = 8.1 Hz, 1H, H-1), 5.53 (d, J = 3.2 Hz, 1H, H-13), 4.74 (d, J = 12.4 Hz, 1H, H-14), 4.60 (d, J = 12.4 Hz, 1H, H-14), 3.96 – 3.75 (m, 7H, H-6, H-19, H-18), 3.14 – 3.02 (m, 1H, H-7), 2.91 (d, J = 9.4 Hz, 1H, H-5), 2.49 – 2.11 (m, 6H, H-2, H-3, H-8, H-9), 1.71 – 1.60 (m, 1H, H-8), 1.54 (s, 3H, H-15), 1.12 (t, J = 12.6 Hz, 1H, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6(C-12), 168.4(C-16), 160.2(C-2', C-6'), 138.8(C-11), 136.5(C-18), 135.5(C-10), 131.7(C-4'), 130.9(C-1), 120.5(C-13), 119.5(C-17), 111.9(C-1'), 103.7(C-3', 5'), 81.2(C-6), 67.1(C-14), 63.4(C-5), 60.1(C-4), 55.9(C-19, C-20), 42.8(C-7), 36.7(C-3), 26.2(C-8), 25.1(C-9), 24.0(C-2), 18.1(C-15). HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ $[M+NH_4]^+$ 472.2330, found 472.2329.

*4.1.5.9 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3,4-dimethoxyphenyl)acrylate (**7e**)*: White solid (yield: 56%), mp 78-80 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 15.9 Hz, 1H, H-18), 7.08 (dd, J = 8.3, 1.7 Hz, 1H, Ar-H), 7.01 (d, J = 1.6 Hz, 1H, Ar-H), 6.86 (d, J = 8.3 Hz, 1H, Ar-H), 6.26 (d, J = 15.9 Hz, 1H, H-17), 6.23 (d, J = 3.5 Hz, 1H, H-13), 5.73 (t, J = 8.1 Hz, 1H, H-1), 5.54 (d, J = 3.1 Hz, 1H, H-13), 4.76 (d, J = 12.5 Hz, 1H, H-14), 4.58 (d, J = 12.5 Hz, 1H, H-14), 3.96 – 3.82 (m, 7H, H-6, Ar-OC<u>H</u>$_3$), 3.07 – 2.95 (m, 1H, H-7), 2.89 (d, J = 9.4 Hz, 1H, H-5), 2.53 – 2.11 (m, 6H, C<u>H</u>$_2$), 1.68 (dd, J = 13.3, 9.0 Hz, 1H,

C<u>H</u>$_2$), 1.54 (s, 3H, H-15), 1.11 (t, *J* = 12.7 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.7(C-16), 151.3(Ar-C), 149.2(Ar-C), 145.4(C-18), 138.8(C-11), 135.0(C-10), 130.7(C-1), 127.0(Ar-C), 122.8(Ar-C), 120.2(C-13), 114.9(C-17), 111.0(Ar-C), 109.4(Ar-C), 81.0(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 55.9(Ar-O<u>C</u>H$_3$), 55.8(Ar-O<u>C</u>H$_3$), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.6(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ $[M+NH_4]^+$ 472.2330, found 472.2333.

*4.1.5.10 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3,5-dimethoxyphenyl)acrylate (**7f**)*: White solid (yield: 73%), mp 134-136 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 15.9 Hz, 1H, H-18), 6.62 (d, *J* = 2.1 Hz, 2H, Ar-H), 6.47 (t, *J* = 2.0 Hz, 1H, Ar-H), 6.36 (d, *J* = 15.9 Hz, 1H, H-17), 6.21 (d, *J* = 3.4 Hz, 1H, H-13), 5.71 (t, *J* = 8.2 Hz, 1H, H-1), 5.54 (d, *J* = 3.4 Hz, 1H, H-13), 4.76 (d, *J* = 12.5 Hz, 1H, H-14), 4.57 (d, *J* = 12.5 Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 3.78 (s, 6H, Ar-OC<u>H</u>$_3$), 3.00 – 2.91 (m, 1H, H-7), 2.86 (d, *J* = 9.4 Hz, 1H, H-5), 2.49 – 2.10 (m, 6H, C<u>H</u>$_2$), 1.73 – 1.62 (m, 1H, C<u>H</u>$_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.3(C-16), 160.9(Ar-C), 145.3(C-18), 138.7(C-11), 135.8(C-10), 134.8(Ar-C), 130.7(C-1), 120.1(C-13), 117.8(C-17), 105.8(Ar-C), 102.7(Ar-C), 80.9(C-6), 66.9(C-14), 63.2(C-5), 59.8(C-4), 55.3(Ar-O<u>C</u>H$_3$), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.5(C-9), 23.7(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ $[M+NH_4]^+$ 472.2330, found 472.2328.

*4.1.5.11 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,3,4-trimethoxyphenyl)acrylate (**7g**)*: White solid (yield: 92%), mp 147-149□. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 16.1 Hz, 1H, H-18), 7.20 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.66 (d, *J* = 8.8 Hz, 1H,

Ar-H), 6.35 (d, *J* = 16.1 Hz, 1H, H-17), 6.18 (d, *J* = 3.4 Hz, 1H, H-13), 5.69 (t, *J* = 8.2 Hz, 1H, H-1), 5.52 (d, *J* = 3.1 Hz, 1H, H-13), 4.73 (d, *J* = 12.5 Hz, 1H, H-14), 4.56 (d, *J* = 12.6 Hz, 1H, H-14), 3.87 (s, 3H, Ar-OC$\underline{H}_3$), 3.85 (s, 3H, Ar-OC$\underline{H}_3$), 3.83 (d, *J* = 4.8 Hz, 4H, H-6, Ar-OC$\underline{H}_3$), 2.96 (dd, *J* = 14.8, 5.8 Hz, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.50 – 2.08 (m, 6H, C$\underline{H}_2$), 1.71 – 1.60 (m, 1H, C$\underline{H}_2$), 1.51 (s, 3H, H-15), 1.07 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.0(C-16), 155.6(Ar-C), 153.1(Ar-C), 142.1(Ar-C), 140.4(C-11), 138.6(C-18), 135.0(C-10), 130.3(C-1), 123.2(Ar-C), 120.9(C-13), 120.1(Ar-C), 115.9(C-17), 107.5(Ar-C), 80.9(C-6), 66.5(C-14), 63.1(C-5), 61.2(Ar-O$\underline{C}H_3$), 60.7(Ar-O$\underline{C}H_3$), 59.8(C-4), 55.9(Ar-O$\underline{C}H_3$), 42.5(C-7), 36.4(C-3), 25.7(C-8), 24.5(C-9), 23.7(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{27}H_{36}NO_8$ $[M+NH_4]^+$ 502.2435, found 502.2444.

*4.1.5.12 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,4,5-trimethoxyphenyl)acrylate (**7h**)*: White solid (yield: 84%), mp 165-167 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 16.1 Hz, 1H, H-18), 6.92 (s, 1H, Ar-H), 6.45 (s, 1H, Ar-H), 6.28 (d, *J* = 16.1 Hz, 1H, H-17), 6.14 (d, *J* = 3.5 Hz, 1H, H-13), 5.68 (t, *J* = 8.1 Hz, 1H, H-1), 5.49 (d, *J* = 3.5 Hz, 1H, H-13), 4.70 (d, *J* = 12.4 Hz, 1H, H-14), 4.54 (d, *J* = 12.4 Hz, 1H, H-14), 3.86 (d, *J* = 9.1 Hz, 3H, Ar-OC$\underline{H}_3$), 3.84 – 3.78 (m, 7H, H-6, Ar-OC$\underline{H}_3$), 3.05 – 2.95 (m, 1H, H-7), 2.85 (d, *J* = 9.4 Hz, 1H, H-5), 2.47 – 2.06 (m, 6H, C$\underline{H}_2$), 1.63 (dd, *J* = 13.1, 9.2 Hz, 1H, C$\underline{H}_2$), 1.50 (s, 3H, H-15), 1.06 (t, *J* = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.1(C-16), 153.9(Ar-C), 152.2(Ar-C), 143.0(Ar-C), 140.2(C-11), 138.6(C-18), 135.0(C-10), 130.5(C-1), 120.0(C-13), 114.4(C-17), 114.2(Ar-C), 110.6(Ar-C), 96.5(Ar-C), 80.9(C-6), 66.6(C-14), 63.1(C-5), 59.8(C-4), 56.2(Ar-O$\underline{C}H_3$), 56.0(Ar-O$\underline{C}H_3$), 55.9(Ar-O$\underline{C}H_3$), 42.5(C-7), 36.4(C-3),

25.7(C-8), 24.6(C-9), 23.6(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{27}H_{36}NO_8$ $[M+NH_4]^+$ 502.2435, found 502.2442.

*4.1.5.13 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,4,6-trimethoxyphenyl)acrylate (**7i**)*: White solid (yield: 77%), mp 194-196 □.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 16.2 Hz, 1H, H-18), 6.68 (d, J = 16.2 Hz, 1H, H-17), 6.17 (d, J = 3.2 Hz, 1H, H-13), 6.08 (s, 2H), 5.71 (t, J = 8.1 Hz, 1H, H-1), 5.52 (d, J = 3.2 Hz, 1H, H-13), 4.71 (d, J = 12.4 Hz, 1H, H-14), 4.57 (d, J = 12.4 Hz, 1H, H-14), 3.84 (m, 10H, H-6, Ar-OC$\underline{H}_3$), 3.14 – 3.03 (m, 1H, H-7), 2.91 (d, J = 9.4 Hz, 1H, H-5), 2.48 – 2.11 (m, 6H, C$\underline{H}_2$), 1.70 – 1.60 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.11 (t, J = 12.6 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5(C-12), 168.6(C-16), 163.0(Ar-C), 161.3(Ar-C), 138.6(C-11), 136.4(C-18), 135.4(C-10), 130.6(C-1), 120.3(C-13), 116.0(C-17), 105.3(Ar-C), 90.2(Ar-C), 81.0(C-6), 66.8(C-14), 63.2(C-5), 59.9(C-4), 55.6(Ar-O$\underline{C}H_3$), 55.3(Ar-O$\underline{C}H_3$), 42.7(C-7), 36.5(C-3), 26.0(C-8), 24.9(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{27}H_{36}NO_8$ $[M+NH_4]^+$ 502.2435, found 502.2444.

*4.1.5.14 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3,4,5-trimethoxyphenyl)acrylate(**7j**)*: white solid (yield: 73%), mp 197-199 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 15.9 Hz, 1H, H-18), 6.68 (s, 2H, Ar-H), 6.27 (d, J = 15.9 Hz, 1H, H-17), 6.16 (d, J = 3.4 Hz, 1H, H-13), 5.69 (t, J = 8.2 Hz, 1H, H-1), 5.50 (d, J = 3.0 Hz, 1H, H-13), 4.72 (d, J = 12.5 Hz, 1H, H-14), 4.55 (d, J = 12.5 Hz, 1H, H-14), 3.82 (m, 10H, H-6, Ar-OC$\underline{H}_3$), 2.97 (dd, J = 14.8, 5.8 Hz, 1H, H-7), 2.84 (d, J = 9.4 Hz, 1H, H-5), 2.49 – 2.07 (m, 6H, C$\underline{H}_2$), 1.66 (dd, J = 16.7, 9.1 Hz, 1H, C$\underline{H}_2$), 1.50 (s, 3H, H-15), 1.06 (t, J = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.3(C-16), 153.2(Ar-C), 145.1(C-18), 140.0(Ar-C), 138.7(C-11),

134.8(C-10), 130.7(C-1), 129.4(Ar-C), 120.0(C-13), 116.4(C-17), 105.0(Ar-C), 80.85(C-6), 66.9(C-14), 63.1(C-5), 60.7(Ar-O<u>C</u>H_3), 59.8(C-4), 55.9(Ar-O<u>C</u>H_3), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.5(C-9), 23.6(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{27}H_{36}NO_8$ $[M+NH_4]^+$ 502.2435, found 502.2445.

*4.1.5.15 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,6-difluorophenyl)acrylate(**7k**)*: White solid (yield: 97%), mp 120-122 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 16.4 Hz, 1H, H-18), 7.37 – 7.27 (m, 1H, Ar-H), 6.93 (t, J = 8.6 Hz, 2H, Ar-H), 6.70 (d, J = 16.4 Hz, 1H, H-17), 6.23 (d, J = 3.4 Hz, 1H, H-13), 5.74 (t, J = 8.3 Hz, 1H, H-1), 5.56 (d, J = 3.4 Hz, 1H, H-13), 4.79 (d, J = 12.5 Hz, 1H, H-14), 4.60 (d, J = 12.5 Hz, 1H, H-14), 3.85 (t, J = 9.3 Hz, 1H, H-6), 2.97 – 2.89 (m, 1H, H-7), 2.87 (d, J = 9.4 Hz, 1H, H-5), 2.51 – 2.11 (m, 6H, C<u>H</u>$_2$), 1.68 (dd, J = 12.8, 9.0 Hz, 1H, C<u>H</u>$_2$), 1.54 (s, 3H, H-15), 1.11 (t, J = 12.9 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 166.4(C-16), 161.6 (dd, J = 255.8, 6.6 Hz, Ar-C), 138.6(C-18), 134.8(C-11), 131.5(C-10), 131.4 (d, J = 11.0 Hz, Ar-C), 130.9(C-1), 123.3 (t, J = 8.8 Hz, Ar-C), 120.3(C-13), 112.4 – 111.4 (m, C17, Ar-C), 80.9(C-6), 67.1(C-14), 63.2(C-5), 59.9(C-4), 42.6(C-7), 36.5(C-3), 25.8(C-8), 24.5(C-9), 23.8(C-2), 17.9(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –109.9 – –110.1 (m). HRMS (ESI) calcd for $C_{24}H_{28}F_2NO_5$ $[M+NH_4]^+$ 448.1930, found 448.1929.

*4.1.5.16 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,6-dichlorophenyl)acrylate(**7l**)*: White solid (yield: 91%), mp 184-186 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 16.4 Hz, 1H, H-18), 7.27 (d, J = 8.1 Hz, 2H, Ar-H), 7.12 (t, J = 8.0 Hz, 1H, Ar-H), 6.51 (d, J = 16.4 Hz, 1H, H-17), 6.14 (d, J = 3.4 Hz, 1H, H-13), 5.68 (t, J = 8.2 Hz,

1H, H-1), 5.49 (d, *J* = 2.4 Hz, 1H, H-13), 4.71 (d, *J* = 12.5 Hz, 1H, H-14), 4.56 (d, *J* = 12.5 Hz, 1H, H-14), 3.79 (t, *J* = 9.3 Hz, 1H, H-6), 2.87 (t, *J* = 9.1 Hz, 1H, H-7), 2.80 (d, *J* = 9.4 Hz, 1H, H-5), 2.44 – 2.04 (m, 6H, C$\underline{H}_2$), 1.69 – 1.57 (m, 1H, C$\underline{H}_2$), 1.47 (s, 3H, H-15), 1.03 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 165.7(C-16), 138.7(C-18), 138.5(C-11), 134.8(Ar-C), 134.6(C-10), 131.3(Ar-C), 131.0(Ar-C), 130.0(C-1), 128.7(Ar-C), 125.8(C-13), 120.2(C-17), 80.8(C-6), 67.1(C-14), 63.1(C-5), 59.8(C-4), 42.5(C-7), 36.4(C-3), 25.6(C-8), 24.4(C-9), 23.7(C-2), 17.8(C-15). HRMS (ESI) calcd for $C_{24}H_{28}Cl_2NO_5$ $[M+NH_4]^+$ 480.1339, found 480.1338.

*4.1.5.17 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,6-dibromophenyl)acrylate(**7m**)*: White solid (yield: 87%), mp 169-171 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.3 Hz, 1H, H-18), 7.58 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.03 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.39 (d, *J* = 16.3 Hz, 1H, H-17), 6.23 (d, *J* = 3.4 Hz, 1H, H-13), 5.76 (t, *J* = 8.2 Hz, 1H, H-1), 5.57 (d, *J* = 3.4 Hz, 1H, H-13), 4.79 (d, *J* = 12.5 Hz, 1H, H-14), 4.65 (d, *J* = 12.5 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 2.93 (dd, *J* = 14.7, 5.8 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.52 – 2.13 (m, 6H, C$\underline{H}_2$), 1.70 (t, *J* = 10.8 Hz, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.12 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 165.5(C-16), 143.1(C-18), 138.6(Ar-C), 135.2(C-11), 134.7(C-10), 132.5(Ar-C), 131.1(Ar-C), 130.6(C-1), 126.1(Ar-C), 123.7(C-13), 120.4(C-17), 80.9(C-6), 67.2(C-14), 63.2(C-5), 59.9(C-4), 42.7(C-7), 36.5(C-3), 25.8(C-8), 24.6(C-9), 23.8(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{24}H_{28}Br_2NO_5$ $[M+NH_4]^+$ 570.0308, found 570.0300.

*4.1.6 General procedure for the synthesis of compounds **10a–10h**.* A mixture of compound **8a** (610 mg, 3.67 mmol, 1 eq), different substituted phenyl acetic acid (3.67 mmol, 1 eq) and

trimethylamine (1 mL) in Ac_2O (20 mL) was refluxed for 4–9 h. After completion of reaction (monitored by TLC), the reaction mixture was cooled and acidified with 35% aqueous HCl (6 mL). The precipitate was collected by filtration and washed by PE: EA= 10: 1. The residue was dissolved in 1 N NaOH and acidified with 35% aqueous HCl, the precipitate was collected by filtration and dried through vacuum. The product acid **9a**–**9h** was directed to next step.

To a solution of compound **2** (53 mg, 0.2 mmol, 1 eq), EDCI (115 mg, 0.6 mmol, 2 eq), DMAP (1.2 mg, 0.01 mmol, 0.05 eq) and corresponded acid (0.3 mmol, 1.5 eq) in CH_2Cl_2 (2 mL) was added Et_3N (83.4 μL, 0.6 mmol, 2 eq) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield compound **10a**–**10h**.

*4.1.6.1 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,5-dimethoxyphenyl)-2-phenylacrylate (**10a**)*: White solid (yield: 86%), mp 90-92 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, H-18), 7.33 (dd, J = 16.1, 8.9 Hz, 3H, Ar-H), 7.19 (d, J = 7.0 Hz, 2H, Ar-H), 6.75 (q, J = 9.0 Hz, 2H, Ar-H), 6.22 (s, 1H, Ar-H), 6.14 (d, J = 2.7 Hz, 1H, H-13), 5.66 (t, J = 7.2 Hz, 1H, H-1), 5.45 (s, 1H, H-13), 4.73 – 4.61 (m, 2H, H-14), 3.88 – 3.75 (m, 4H, H-16, OC$\underline{H}_3$), 3.23 (s, 3H, OC$\underline{H}_3$), 2.83 (d, J = 8.4 Hz, 1H, H-7), 2.76 (d, J = 9.3 Hz, 1H, H-5), 2.47 – 2.08 (m, 6H, C$\underline{H}_2$), 1.64 – 1.54 (m, 1H, C$\underline{H}_2$), 1.51 (s, 3H, H-15), 1.07 (t, J = 12.4 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.4(C-16), 152.8(Ar-C), 152.4(Ar-C), 138.8(C-18), 136.0(Ar-C), 135.3(C-11), 134.8(C-10), 131.6(C-17), 130.7(C-1), 129.7(Ar-C), 128.6(Ar-C), 127.7(Ar-C), 123.3(Ar-C), 120.0(C-13), 117.6(Ar-C), 114.1(Ar-C), 111.8(Ar-C), 80.7(C-6), 67.2(C-14),

63.1(C-5), 59.9(C-4), 56.0(Ar-O<u>C</u>H_3), 55.0(Ar-O<u>C</u>H_3), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.9(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{32}H_{38}NO_7$ $[M+NH_4]^+$ 548.2643, found 548.2642.

*4.1.6.2 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,5-dimethoxyphenyl)-2-(4-(trifluoromethyl)phenyl)acrylate (**10b**)*: yellow solid (yield: 65%), mp 79-81 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, H-18), 7.61 (d, J = 8.1 Hz, 2H, Ar-H), 7.35 (d, J = 8.1 Hz, 2H, Ar-H), 6.82 – 6.73 (m, 2H, Ar-H), 6.16 (d, J = 3.4 Hz, 1H, H-13), 6.09 (s, 1H, Ar-H), 5.68 (t, J = 7.9 Hz, 1H, H-1), 5.48 (d, J = 3.0 Hz, 1H, H-13), 4.75 – 4.65 (m, 2H, H-14), 3.86 – 3.78 (m, 4H, H-6, OC<u>H</u>$_3$), 3.24 (s, 3H, OC<u>H</u>$_3$), 2.91 (ddd, J = 12.0, 9.2, 3.1 Hz, 1H, H-7), 2.83 (d, J = 9.4 Hz, 1H, H-5), 2.48 – 2.11 (m, 6H, C<u>H</u>$_2$), 1.70 – 1.59 (m, 1H, C<u>H</u>$_2$), 1.53 (s, 3H, H-15), 1.08 (t, J = 12.5 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, CDCl3) δ 169.3(C-12), 166.7(C-16), 152.8(Ar-C), 152.5(Ar-C), 140.0(C-18), 138.6(Ar-C), 137.0(C-11), 133.9(C-10), 131.9 (d, J = 137.5 Hz, Ar-C), 130.8(C-17), 130.5(C-1), 130.2(Ar-C), 127.1(Ar-C), 125.4 (d, J = 3.7 Hz, Ar-C), 121.2 (d, J = 313.5 Hz, CF_3), 120.3(C-13), 118.1(Ar-C), 114.8 (d, J = 14.8 Hz, Ar-C), 114.1(Ar-C), 112.0(Ar-C), 111.5(Ar-C), 80.8(C-6), 67.4(C-14), 63.2(C-5), 59.9(C-4), 56.0(Ar-O<u>C</u>H_3), 55.0(Ar-O<u>C</u>H_3), 42.7(C-7), 36.6(C-3), 25.7(C-8), 24.7(C-9), 23.8(C-2), 18.0(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (s). HRMS (ESI) calcd for $C_{33}H_{33}F_3NaO_7$ $[M+Na]^+$ 621.2071, found 621.2073.

*4.1.6.3 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2,5-dimethoxyphenyl)-2-(4-fluorophenyl)acrylate (**10c**)*: White solid (yield: 70%), mp 83-85 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H, H-18), 7.18 (dd, J = 8.4, 5.5 Hz, 2H, Ar-H), 7.04 (t, J = 8.4 Hz, 2H, Ar-H),

6.81 – 6.74 (m, 2H, Ar-H), 6.22 (s, 1H, Ar-H), 6.17 (d, *J* = 3.0 Hz, 1H, H-13), 5.69 (t, *J* = 7.8 Hz, 1H, H-1), 5.47 (d, *J* = 3.0 Hz, 1H, H-13), 4.74 – 4.64 (m, 2H, H-14), 3.87 – 3.79 (m, 4H, H-6, OC$\underline{H}_3$), 3.33 (s, 3H, OC$\underline{H}_3$), 2.98 – 2.87 (m, 1H, H-7), 2.84 (t, *J* = 8.2 Hz, 1H, H-5), 2.48 – 2.12 (m, 6H, C$\underline{H}_2$), 1.68 – 1.59 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.10 (t, *J* = 12.5 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.3(C-12), 167.2(C-16), 162.2 (d, *J* = 247.5 Hz, Ar-C), 152.7(Ar-C), 152.5(Ar-C), 138.7(C-18), 136.0(C-11), 134.8(C-17), 131.8(C-10), 131.7 (d, *J* = 8.0 Hz, Ar-C), 130.7(Ar-C), 130.6(C-1), 123.3(Ar-C), 120.2(C-13), 117.4(Ar-C), 115.6 (d, *J* = 21.4 Hz, Ar-C), 114.4(Ar-C), 111.8(Ar-C), 80.8(C-6), 67.3(C-14), 63.2(C-5), 59.9(C-5), 56.0(Ar-O$\underline{C}H_3$), 55.1(Ar-O$\underline{C}H_3$), 42.7(C-7), 36.6(C-3), 25.7(C-8), 24.8(C-9), 23.8(C-2), 17.9(C-15). ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -113.72 – -113.81 (m). HRMS (ESI) calcd for $C_{32}H_{37}FNO_7$ $[M+NH_4]^+$ 566.2549, found 566.2548.

*4.1.6.4 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-2-(4-chlorophenyl)-3-(2,5-dimethoxyphenyl)acrylate (**10d**)*: White solid (yield: 77%), mp 153-155 □. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.14 (s, 1H, H-18), 7.34 – 7.28 (m, 2H, Ar-H), 7.14 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.80 – 6.74 (m, 2H, Ar-H), 6.19 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.16 (d, *J* = 3.4 Hz, 1H, H-13), 5.68 (t, *J* = 7.9 Hz, 1H, H-1), 5.47 (d, *J* = 3.0 Hz, 1H, H-13), 4.74 – 4.60 (m, 2H, H-14), 3.89 – 3.77 (m, 4H, H-6, OC$\underline{H}_3$), 3.33 (s, 3H, OC$\underline{H}_3$), 2.96 – 2.86 (m, 1H, H-7), 2.82 (d, *J* = 9.4 Hz, 1H, H-5), 2.46 – 2.11 (m, 6H, C$\underline{H}_2$), 1.67 – 1.59 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (dd, *J* = 15.4, 9.8 Hz, 1H, C$\underline{H}_2$).^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.2(C-12), 166.9(C-16), 152.7(Ar-C), 152.4(Ar-C), 138.6(C-18), 136.2(C-11), 134.7(C-10), 134.3(C-17), 133.7(Ar-C), 131.3(Ar-C), 130.7(C-1), 130.4(Ar-C), 128.7(Ar-C), 123.1(Ar-C), 120.2(C-13), 117.4(Ar-C), 114.3(Ar-C), 111.8(Ar-C), 80.8(C-6), 67.3(C-14), 63.1(C-5), 59.9(C-4), 56.0(Ar-O$\underline{C}H_3$), 55.0(Ar-O$\underline{C}H_3$), 42.6(C-7),

36.5(C-3), 25.6(C-8), 24.7(C-9), 23.7(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{32}H_{37}ClNO_7$ $[M+NH_4]^+$ 582.2253, found 582.2246.

*4.1.6.5 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-2-(4-bromophenyl)-3-(2,5-dimethoxyphenyl)acrylate (**10e**)*: White solid (yield: 84%), mp 78-80 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H, H-18), 7.46 (d, J = 8.2 Hz, 2H, Ar-H), 7.08 (d, J = 8.2 Hz, 2H, Ar-H), 6.79 (d, J = 17.3 Hz, 2H, Ar-H), 6.19 (s, 1H, Ar-H), 6.16 (d, J = 3.2 Hz, 1H, H-13), 5.67 (t, J = 7.7 Hz, 1H, H-1), 5.47 (d, J = 2.7 Hz, 1H, H-13), 4.72 – 4.62 (m, 2H, H-14), 3.87 – 3.75 (m, 4H, H-6, OC<u>H</u>$_3$), 3.32 (s, 3H, OC<u>H</u>$_3$), 2.89 (t, J = 8.7 Hz, 1H, H-7), 2.82 (d, J = 9.4 Hz, 1H, H-5), 2.48 – 2.10 (m, 6H, C<u>H</u>$_2$), 1.63 (m, 1H, C<u>H</u>$_2$), 1.52 (s, 3H, H-15), 1.08 (t, J = 12.5 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 166.8(C-16), 152.7(Ar-C), 152.4(Ar-C), 138.6(C-18), 136.2(C-11), 134.8(C-10), 134.7(C-17), 131.6(Ar-C), 130.7(C-1), 130.4(Ar-C), 128.2(Ar-C), 123.0(Ar-C), 121.8(Ar-C), 120.2(C-13), 117.5(Ar-C), 114.3(Ar-C), 111.8(Ar-C), 80.8(C-6), 67.3(C-14), 63.1(C-5), 59.9(C-4), 55.9(Ar-O<u>C</u>H$_3$), 55.0(Ar-O<u>C</u>H$_3$), 42.6(C-7), 36.5(C-3), 25.6(C-8), 24.7(C-9), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{32}H_{37}BrNO_7$ $[M+NH_4]^+$ 626.1748, found 626.1749.

*4.1.6.6 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)-2-(p-tolyl)acrylate (**10f**)*: White solid (yield: 93%), mp 81-83 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, H-18), 7.09 (dd, J = 30.5, 7.7 Hz, 4H, Ar-H), 6.78 – 6.69 (m, 2H, Ar-H), 6.25 (s, 1H, Ar-H), 6.12 (d, J = 3.0 Hz, 1H, H-13), 5.66 (t, J = 7.9 Hz, 1H, H-1), 5.43 (d, J = 2.5 Hz, 1H, H-13), 4.64 (dd, J = 27.6, 12.4 Hz, 2H, H-14), 3.80 (s, 3H, OC<u>H</u>$_3$), 3.76 (d, J = 9.3 Hz, 1H, H-6), 3.24 (s, 3H, OC<u>H</u>$_3$), 2.80 (t, J = 8.8 Hz, 1H, H-7), 2.73 (d, J = 9.4 Hz, 1H, H-5), 2.44 – 2.33 (m,

1H, C<u>H</u>$_2$), 2.32 (s, 3H, Ar-C<u>H</u>$_3$), 2.27 – 2.09 (m, 5H, C<u>H</u>$_2$), 1.63 – 1.53 (m, 1H, C<u>H</u>$_2$), 1.50 (s, 3H, H-15), 1.06 (t, *J* = 12.5 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.2(C-12), 167.5(C-16), 152.7(Ar-C), 152.3(Ar-C), 138.8(C-18), 137.5(Ar-C), 135.0(C-11), 134.8(C-10), 132.8(Ar-C), 131.6(C-17), 130.8(C-1), 129.5(Ar-C), 129.2(Ar-C), 123.5(Ar-C), 119.9(C-13), 117.3(Ar-C), 114.1(Ar-C), 111.7(Ar-C), 80.6(C-6), 67.2(C-14), 63.0(C-5), 59.8(C4), 55.9(Ar-O<u>C</u>H$_3$), 54.8(Ar-O<u>C</u>H$_3$), 42.5(C-7), 36.5(C-3), 25.7(C-8), 25.0(C-9), 23.6(C-2), 21.1(Ar-<u>C</u>H$_3$), 17.9(C-15). HRMS (ESI) calcd for $C_{33}H_{40}NO_7$ $[M+NH_4]^+$ 562.2799, found 562.2797.

*4.1.6.7 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylate (**10g**)*: White solid (yield: 83%), mp 89-91 □. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.10 (s, 1H, H-18), 7.11 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.86 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.83 – 6.70 (m, 2H, Ar-H), 6.30 (d, *J* = 2.4 Hz, 1H, Ar-H), 6.15 (d, *J* = 3.4 Hz, 1H, H-13), 5.69 (t, *J* = 7.9 Hz, 1H, H-1), 5.45 (d, *J* = 3.0 Hz, 1H, H-13), 4.66 (q, *J* = 12.4 Hz, 2H, H-14), 3.80 (m, 7H, H-6, OC<u>H</u>$_3$), 3.31 (s, 3H, OC<u>H</u>$_3$), 2.91 – 2.82 (m, 1H, H-7), 2.77 (d, *J* = 9.4 Hz, 1H, H-5), 2.46 – 2.11 (m, 6H, C<u>H</u>$_2$), 1.66 – 1.56 (m, 1H, C<u>H</u>$_2$), 1.52 (s, 3H, H-15), 1.08 (t, *J* = 12.4 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.3(C-12), 167.7(C-16), 159.1(Ar-C), 152.7(Ar-C), 152.4(Ar-C), 138.8(C-18), 135.1(C-11), 134.9(C-10), 131.3(C-17), 131.0(Ar-C), 131.0(C-1), 127.9(Ar-C), 123.7(Ar-C), 120.1(C-13), 117.2(Ar-C), 114.3(Ar-C), 114.0(Ar-C), 111.8(Ar-C), 80.7(C-6), 67.3(C-14), 63.1(C-5), 59.9(C-4), 56.0(Ar-O<u>C</u>H$_3$), 55.2(Ar-O<u>C</u>H$_3$), 55.1(Ar-O<u>C</u>H$_3$), 42.6(C-7), 36.6(C-3), 25.8(C-8), 25.1(C-9), 23.7(C-2), 18.0(C-15). HRMS (ESI) calcd for $C_{33}H_{40}NO_8$ $[M+NH_4]^+$ 578.2748, found 578.2742.

4.1.6.8 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)-2-

*(4-ethoxyphenyl)acrylate (**10h**)*: White solid (yield: 84%), mp 106-109 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H, H-18), 7.09 (d, J = 8.6 Hz, 2H, Ar-H), 6.85 (d, J = 8.6 Hz, 2H, Ar-H), 6.80 – 6.70 (m, 2H, Ar-H), 6.32 (d, J = 2.4 Hz, 1H, Ar-H), 6.15 (d, J = 3.4 Hz, 1H, H-13), 5.69 (t, J = 7.9 Hz, 1H, H-1), 5.46 (d, J = 3.0 Hz, 1H, H-13), 4.72 – 4.61 (m, 2H, H-14), 4.02 (q, J = 6.6 Hz, 2H, Ar-OC$\underline{H}_2$CH$_3$), 3.86 – 3.76 (m, 4H, OC$\underline{H}_3$), 3.31 (s, 3H, OC$\underline{H}_3$), 2.93 – 2.83 (m, 1H, H-7), 2.79 (d, J = 9.4 Hz, 1H, H-5), 2.43 – 2.12 (m, 6H, C$\underline{H}_2$), 1.66 – 1.56 (m, 1H, C$\underline{H}_2$), 1.52 (s, 3H, H-5), 1.40 (t, J = 6.9 Hz, 3H, Ar-OCH$_2$C$\underline{H}_3$), 1.09 (dd, J = 15.6, 9.0 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.7(C-16), 158.5(Ar-C), 152.7(Ar-C), 152.4(Ar-C), 138.8(C-18), 135.0(C-11), 134.9(C-10), 131.4(C-17), 131.0(Ar-C), 130.8(C-1), 127.7(Ar-C), 123.7(Ar-C), 120.1(C-13), 117.2(Ar-C), 114.6(Ar-C), 114.2(Ar-C), 111.8(Ar-C), 80.8(C-6), 67.3(C-14), 63.4(Ar-O$\underline{C}$H$_2$CH$_3$), 63.1(C-5), 59.9(C-4), 56.0(Ar-O$\underline{C}$H$_3$), 55.1(Ar-O$\underline{C}$H$_3$), 42.6(C-7), 36.6(C-3), 25.8(C-8), 25.0(C-9), 23.7(C-2), 18.0(C-15), 14.8(Ar-OCH$_2\underline{C}$H$_3$). HRMS (ESI) calcd for $C_{34}H_{38}NaO_8$ $[M+Na]^+$ 597.2459, found 597.2462.

*4.1.6.9 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)-2-(4-(methylthio)phenyl)acrylate (**10i**)*: White solid (yield: 90%), mp 187-189 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, H-18), 7.20 (d, J = 8.2 Hz, 2H, Ar-H), 7.10 (d, J = 8.1 Hz, 2H, Ar-H), 6.78 – 6.71 (m, 2H, Ar-H), 6.25 (d, J = 1.8 Hz, 1H, Ar-H), 6.14 (d, J = 3.2 Hz, 1H, H-13), 5.67 (t, J = 7.8 Hz, 1H, H-1), 5.45 (d, J = 2.8 Hz, 1H, H-13), 4.65 (q, J = 12.5 Hz, 2H, H-14), 3.85 – 3.75 (m, 4H, H-6, OC$\underline{H}_3$), 3.29 (s, 3H, OC$\underline{H}_3$), 2.85 (dd, J = 15.5, 8.8 Hz, 1H, H-7), 2.76 (d, J = 9.4 Hz, 1H, H-5), 2.47 (d, J = 7.3 Hz, 3H, SC$\underline{H}_3$), 2.42 – 2.08 (m, 6H, C$\underline{H}_2$), 1.61 (dd, J = 19.2, 7.5 Hz, 1H, C$\underline{H}_2$), 1.51 (s, 3H, H-15), 1.07 (t, J = 12.4 Hz, 1H, C$\underline{H}_2$).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 167.3(C-16), 152.7(Ar-C), 152.4(Ar-C), 138.7(C-18), 138.3(C-11),

135.5(C-10), 134.7(C-17), 132.3(Ar-C), 131.0(Ar-C), 130.8(C-1), 130.2(Ar-C), 126.3(Ar-C), 123.3(Ar-C), 120.1(C-13), 117.4(Ar-C), 114.1(Ar-C), 111.7(Ar-C), 80.7(C-6), 67.2(C-14), 63.0(C-5), 59.8(C-4), 56.0(Ar-O$\underline{C}H_3$), 55.0(Ar-O$\underline{C}H_3$), 42.5(C-7), 36.5(C-3), 25.6(C-8), 24.9(C-9), 23.7(C-2), 17.9(C-15), 15.4(S$\underline{C}H_3$). HRMS (ESI) calcd for $C_{33}H_{40}NO_7S$ $[M+NH_4]^+$ 594.2520, found 594.2516.

*4.1.7 General procedure for the synthesis of compounds **12a–12c.***

The aldehyde **8a** (498 mg, 3.0 mmol, 1 eq) and different substituted malonic acid (6.0 mmol, 2 eq) were dissolved in pyridine (30 mL) and piperidine (0.5 mL) was added. The mixture was heated to reflux overnight. After cooling down to room temperature the reaction mixture was poured into ice cold conc. HCl. The precipitate was collected and dried in vacuo. The product acid **11a**–**11c** was directed to next step. To a solution of compound **2** (53 mg, 0.2 mmol, 1 eq), EDCI (115 mg, 0.6 mmol, 2 eq), DMAP (1.2 mg, 0.01 mmol, 0.05 eq) and corresponded acid **11a**–**11c** (0.3 mmol, 1.5 eq) in CH_2Cl_2 (2 mL) was added Et_3N (83.4 μL, 0.6 mmol, 2 eq) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield compounds **12a**–**12c**.

*4.1.7.1 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)-2-methylacrylate (**12a**)*: White solid (yield: 95%), mp 139-141 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H, H-18), 6.92 – 6.75 (m, 3H, Ar-H), 6.15 (d, J = 3.1 Hz, 1H, H-13), 5.72 (t, J = 8.1 Hz, 1H, H-1), 5.51 (d, J = 2.7 Hz, 1H, H-13), 4.72 (d, J = 12.5 Hz, 1H, H-14), 4.61 (d, J = 12.5

Hz, 1H, H-14), 3.84 (t, *J* = 9.3 Hz, 1H, H-6), 3.77 (s, 3H, OC$\underline{H}_3$), 3.75 (s, 3H, OC$\underline{H}_3$), 2.96 (t, *J* = 9.0 Hz, 1H, H-7), 2.88 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.10 (m, 6H, C$\underline{H}_2$), 2.03 (s, 3H, CH=CC$\underline{H}_3$), 1.67 (dd, *J* = 16.2, 8.2 Hz, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, *J* = 12.9 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.2(C-12), 168.0(C-16), 152.8(Ar-C), 151.8(Ar-C), 138.6(C-11), 135.0(C-18), 135.0(C-10), 130.4(C-1), 128.0(C-17), 125.0(C-13), 120.2(Ar-C), 115.9(Ar-C), 114.4(Ar-C), 111.3(Ar-C), 80.8(C-6), 66.9(C-14), 63.1(C-5), 59.9(C-4), 55.8(Ar-O$\underline{C}$H3), 55.6(Ar-O$\underline{C}$H3), 42.6(C-7), 36.5(C-3), 25.7(C-8), 24.6(C-9), 23.7(C-2), 17.9(C-15), 14.1(CH=C$\underline{C}H_3$). HRMS (MALDI) calcd for $C_{27}H_{32}NaO_7$ $[M+Na]^+$ 491.2040, found 491.2045.

*4.1.7.2 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl 2-((E)-2,5-dimethoxybenzylidene)butanoate (**12b**)*: White solid (yield: 73%), mp 131-134 □. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.75 (s, 1H, H-18), 6.91 – 6.79 (m, 3H, Ar-H), 6.19 (d, *J* = 3.5 Hz, 1H, H-13), 5.75 (t, *J* = 8.2 Hz, 1H, H-1), 5.53 (d, *J* = 3.1 Hz, 1H, H-13), 4.77 (d, *J* = 12.6 Hz, 1H, H-14), 4.63 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.78 (d, *J* = 6.0 Hz, 6H, OC$\underline{H}_3$), 3.02 – 2.93 (m, 1H, H-7), 2.91 (d, *J* = 9.4 Hz, 1H, H-5), 2.55 – 2.14 (m, 8H, C$\underline{H}_2$, CH=CC$\underline{H}_2$CH$_3$), 1.74 – 1.65 (m, 1H, C$\underline{H}_2$), 1.56 (s, 3H, H-15), 1.20 – 1.08 (m, 4H, C$\underline{H}_2$, CH=CCH$_2$C$\underline{H}_3$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.3(C-12), 167.7(C-16), 153.0(Ar-C), 151.8(Ar-C), 138.6(C-11), 135.1(C-18), 134.9(C-10), 134.4(C-17), 130.5(C-1), 125.1(Ar-C), 120.4(C-13), 115.3(Ar-C), 114.5(Ar-C), 111.4(Ar-C), 80.9(C-6), 66.9(C-14), 63.3(C-5), 60.0(C-4), 56.0(Ar-O$\underline{C}$H3), 55.7(Ar-O$\underline{C}$H3), 42.7(C-7), 36.6(C-3), 25.8(C-8), 24.7(C-9), 23.8(C-2), 21.1(C-15), 18.0(CH=$\underline{C}$H$_2$CH$_3$), 14.0(CH=CH$_2\underline{C}$H$_3$). HRMS (MALDI) calcd for $C_{28}H_{34}NaO_7$ $[M+Na]^+$505.2197, found 505.2198.

*4.1.7.3 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl 2-((E)-2,5-dimethoxybenzylidene)pentanoate (**12c**)*: White solid (yield: 54%), mp 127-129 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H, H-18), 6.88-6.81 (m, 3H, Ar-H), 6.19 (d, *J* = 3.4 Hz, 1H, H-13), 5.74 (t, *J* = 8.3 Hz, 1H, H-1), 5.52 (d, *J* = 3.1 Hz, 1H, H-13), 4.75 (d, *J* = 12.6 Hz, 1H, H-14), 4.63 (d, *J* = 12.6 Hz, 1H, H-14), 3.86 (t, *J* = 9.3 Hz, 1H, H-6), 3.78 (d, *J* = 6.0 Hz, 6H, $OC\underline{H}_3$), 3.02 – 2.93 (m, 1H, H-7), 2.90 (d, *J* = 9.4 Hz, 1H, H-5), 2.53 – 2.14 (m, 8H, $C\underline{H}_2$, $CH{=}CC\underline{H}_2CH_2CH_3$), 1.75 – 1.64 (m, 1H, $C\underline{H}_2$), 1.60 – 1.49 (m, 5H, H-15, $CH{=}CCH_2C\underline{H}_2CH_3$), 1.13 (t, *J* = 12.7 Hz, 1H, $C\underline{H}_2$), 0.94 (t, *J* = 7.3 Hz, 3H, $CH{=}CCH_2CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3(C-12), 167.9(C-16), 153.0(Ar-C), 151.9(Ar-C), 138.6(C-11), 135.2(C-18), 135.1(C-10), 133.1(C-17), 130.3(C-1), 125.1(Ar-C), 120.3(C-13), 115.1(Ar-C), 114.8(Ar-C), 111.5(Ar-C), 80.9(C-6), 66.9(C-14), 63.3(C-5), 60.0(C-4), 56.0(Ar-$O\underline{C}H_3$), 55.7(Ar-$O\underline{C}H_3$), 42.7(C-7), 36.6(C-3), 29.9($CH{=}C\underline{C}H_2CH_2CH_3$), 25.8(C-8), 24.7(C-9), 23.8(C-2), 22.7($CH{=}CCH_2\underline{C}H_2CH_3$), 18.0(C-15), 14.2($CH{=}CCH_2CH_2\underline{C}H_3$). HRMS (ESI) calcd for $C_{29}H_{36}NaO_7$ $[M+Na]^+$ 519.2353, found 519.2358.

*4.1.8 The synthesis of ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-2-cyano-3-(2,5-dimethoxyphenyl)acrylate (**14**):* The aldehyde **8a** (498 mg, 3.0 mmol, 1 eq) and cyanoacetic acid (378 mg, 4.5 mmol, 1.5 eq) were dissolved in pyridine(30 mL) and piperidine (0.5 mL) was added. The mixture was heated to reflux overnight. After cooling down to room temperature the reaction mixture was poured into ice cold conc. HCl. The precipitate was collected and dried in vacuo. The product acid **13** was directed to next step. To a solution of **2** (47.6 mg, 0.18 mmol), EDCI (101.6 mg, 0.53 mmol), DMAP (2.2 mg, 0.018 mmol) and **13** (62.9

mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (74 μL, 0.53 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE:EA = 3:1] to yield compound **14** (71 mg, 83%) as yellow solid, mp 178-180 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, H-18), 7.26 (s, 1H, Ar-H), 7.10 (dd, *J* = 9.1, 3.0 Hz, 1H, Ar-H), 6.90 (d, *J* = 9.2 Hz, 1H, Ar-H), 6.22 (d, *J* = 3.4 Hz, 1H, H-13), 5.78 (t, *J* = 8.3 Hz, 1H, H-1), 5.56 (d, *J* = 3.0 Hz, 1H, H-13), 4.81 (d, *J* = 12.4 Hz, 1H, H-14), 4.75 (d, *J* = 12.4 Hz, 1H, H-14), 3.95 – 3.84 (m, 4H, H-6, OC$\underline{H}_3$), 3.81 (s, 3H, OC$\underline{H}_3$), 2.93 (dd, *J* = 15.6, 6.4 Hz, 1H, H-7), 2.87 (d, *J* = 9.4 Hz, 1H, H-5), 2.52 – 2.14 (m, 6H, C$\underline{H}_2$), 1.78 – 1.67 (m, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.12 (t, *J* = 12.8 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C-12), 162.6(C-16), 154.1(Ar-C), 153.3(Ar-C), 150.0(C-18), 138.5(C-11), 134.1(C-10), 131.4(C-1), 122.9(C-13), 120.4(Ar-C), 120.3(CN), 115.8(Ar-C), 112.5(Ar-C), 111.9(Ar-C), 101.0(C-17), 80.9(C-6), 68.3(C-14), 63.2(C-5), 59.9(C-4), 56.2(Ar-O$\underline{C}H_3$), 55.8(Ar-O$\underline{C}H_3$), 42.6(C-7), 36.5(C-3), 25.5(C-8), 24.3(C-9), 23.8(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{27}H_{29}NNaO_7$ $[M+Na]^+$ 5052.1836, found 5052.1840.

*4.1.9 The synthesis of compounds 16 (1aR,7aS,8S,10aS,10bS,E)-5-(Hydroxymethyl)-1a,8-dimethyl-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one **(15)**:* To a solution of compound **2** (400 mg, 1.51 mmol) in EtOH (12 mL)was added $NaBH_4$ (63 mg, 1.67 mmol) at 0 ^{0}C, the mixture was stirred for 4h at the room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE:EA=1:1] to yield compound

15 (311 mg, 77%), as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (t, J = 7.8 Hz, 1H, H-1), 4.08 (q, J = 12.5 Hz, 2H, H-14), 3.83 (t, J = 9.5 Hz, 1H, H-6), 2.75 (d, J = 9.4 Hz, 1H, H-5), 2.50 – 2.08 (m, 7H, C$\underline{H}_2$, C$\underline{H}$), 1.90 (td, J = 12.1, 2.5 Hz, 1H, C$\underline{H}_2$), 1.68 – 1.46 (m, 5H, H-15, C$\underline{H}_2$, C$\underline{H}$), 1.25 (d, J = 6.9 Hz, 3H, H-13), 1.07 (t, J = 12.5 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0(C-12), 139.9(C-10), 127.3(C-1), 81.3(C-6), 65.9(C-14), 63.7(C-5), 60.0(C-4), 46.6(C-11), 41.6(C-7), 37.1(C-3), 26.8(C-8), 24.3(C-9), 23.7(C-2), 18.0(C-15), 13.2(C-13). HRMS (ESI) calcd for $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1410, found 289.1413.

*4.1.10 The synthesis of ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl 2,6-dimethoxybenzoate (**16**):* To a solution of **2** (82.6 mg, 0.31 mmol), EDCI (89.9 mg, 0.47 mmol), DMAP (3.8 mg, 0.03 mmol) and 2,6-dimethoxybenzoic acid (85.5 mg, 0.47 mmol) in CH_2Cl_2 (1 mL) was added TEA (65 uL , 0.47 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE:EA=3:1] to yield compound **16** (71 mg, 83%), as a white solid, mp 101-103 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 1H, Ar-H), 6.55 (d, J = 8.4 Hz, 2H, Ar-H), 6.11 (d, J = 2.9 Hz, 1H, H-13), 5.81 (t, J = 7.9 Hz, 1H, H-1), 5.41 (d, J = 2.1 Hz, 1H, H-13) , 5.11 (d, J = 12.4 Hz, 1H, H-14), 4.54 (d, J = 12.4 Hz, 1H, H-14), 3.90 – 3.72 (m, 7H, H-6, OC$\underline{H}_3$), 2.99 (t, J = 9.0 Hz, 1H, H-7), 2.90 (d, J = 9.4 Hz, 1H, H-5), 2.57 – 2.13 (m, 6H, C$\underline{H}_2$), 1.63 (t, J = 10.6 Hz, 1H, C$\underline{H}_2$), 1.55 (s, 3H, H-15), 1.13 (t, J = 12.7 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7(C-12), 166.3(C-16), 157.4(Ar-C), 138.7(C-11), 135.3(C-10), 131.4(Ar-C), 131.2(C-1), 120.3(C-13), 112.8(Ar-C), 104.1(Ar-C), 81.3(C-6), 68.0(C-14), 63.5(C-5), 60.1(C-

4), 56.1(Ar-O<u>C</u>H$_3$), 42.7(C-7), 36.8(C-13), 26.0(C-8), 24.7(C-9), 24.1(C-2), 18.2(C-15). HRMS (ESI) calcd for $C_{24}H_{28}NaO_7$ $[M+Na]^+$ 451.1727, found 451.1732.

*4.1.11 General procedure for the synthesis of compounds **17a** and **17b**.*

The aldehyde **8a** or **8b** (500 mg, 3.0 mmol, 1 eq) and malonic acid (469.6 mg, 4.51 mmol, 1.5 eq) were dissolved in pyridine (30 mL) and piperidine (274 μL, 3.0 mmol, 1 eq) was added. The mixture was heated to reflux overnight. After cooling down to room temperature the reaction mixture was poured into ice cold conc. HCl. The precipitate **17a** and **17b** was collected and dried in vacuo.

*4.1.11.1 (E)-3-(2, 5-Dimethoxyphenyl) acrylic acid (**17a**)*: white solid (yield: 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H, COOH), 7.80 (d, J = 16.1 Hz, 1H, H-18), 7.25 (s, 1H, Ar-H), 7.07 – 6.93 (m, 2H, Ar-H), 6.55 (d, J = 16.1 Hz, 1H, H-17), 3.80 (s, 3H, OC<u>H</u>$_3$), 3.74 (s, 3H, OC<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9(<u>C</u>OOH), 153.2(Ar-C), 152.1(Ar-C), 138.4(<u>C</u>H=CH), 123.0(Ar-C), 119.6(Ar-C), 117.5(<u>C</u>H=CH), 113.0(Ar-C), 112.6(Ar-C), 56.1(Ar-O<u>C</u>H$_3$), 55.6(Ar-O<u>C</u>H$_3$). HRMS (ESI) calcd for $C_{11}H_{11}O_4$ $[M–H]^-$ 207.0663, found 207.0660.

*4.1.11.2 (E)-3-(2, 6-Dimethoxyphenyl)acrylic acid (**17b**)*: white solid (yield: 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H, COOH), 7.94 (d, J = 16.3 Hz, 1H, H-18), 7.34 (t, J = 8.4 Hz, 1H, Ar-H), 6.71 (dd, J = 16.3, 8.4 Hz, 3H, Ar-H, H-17), 3.85 (s, 6H, OC<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9(<u>C</u>OOH), 159.54(Ar-C), 134.7(<u>C</u>H=CH), 131.9(Ar-C), 120.9(<u>C</u>H=CH), 110.9(Ar-C), 104.1(Ar-C), 56.0(Ar-O<u>C</u>H$_3$). HRMS (ESI) calcd for $C_{11}H_{12}NaO_4$ $[M+Na]^+$ 231.0628, found 231.0631.

*4.1.12 General procedure for the synthesis of compounds **19a** and **19b**.*

The mixture of **17a** or **17b** (320 mg, 1.54 mmol) and 3.0 mL thionyl chloride was dissolved in DCM (15 mL) and refluxed at 75 °C for 2 h. The excess thionyl chloride was removed under reduced pressure. After the residue was dissolved in 10 mL DCM, the methanol 10ml was added at 0 °C. The solution was stirred at 0 °C for 1 h and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (PE: EA=5:1) to afford the desired product.

*4.1.12.1 Methyl (E)-3-(2,5-Dimethoxyphenyl) acrylate (**19a**)*: white solid (yield: 75%), mp 72-74 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 16.2 Hz, 1H, H-18), 7.03 (d, J = 2.7 Hz, 1H, Ar-H), 6.90 (dd, J = 9.0, 2.8 Hz, 1H, Ar-H), 6.83 (d, J = 9.0 Hz, 1H, Ar-H), 6.49 (d, J = 16.2 Hz, 1H, H-17), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7(C=O), 153.4(Ar-C), 152.7(Ar-C), 139.9(CH=CH), 123.8(CH=CH), 118.4(Ar-C), 117.0(Ar-C), 113.2(Ar-C), 112.3(Ar-C), 56.0(Ar- OCH_3), 55.7(Ar- OCH_3), 51.6(O=COCH_3). HRMS (ESI) calcd for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0965, found 223.0966.

*4.1.12.2 Methyl (E)-3-(2, 6-Dimethoxyphenyl) acrylate (**19b**)*: white s solid (yield: 81%), mp 81-83 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 16.3 Hz, 1H, H-18), 7.27 (t, J = 8.4 Hz, 1H, Ar-H), 6.89 (d, J = 16.3 Hz, 1H, H-17), 6.56 (d, J = 8.4 Hz, 2H, Ar-H), 3.88 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2(C=O), 160.2(Ar-C), 135.8(CH=CH), 131.4(Ar-C), 120.4(CH=CH), 112.3(Ar-C), 103.8(Ar-C), 55.9(Ar- OCH_3), 51.6(O=COCH_3). HRMS (ESI) calcd for $C_{12}H_{14}NaO_4$ $[M+Na]^+$ 245.0784, found 245.0788.

*4.1.13 General procedure for the synthesis of compounds **20a** and **20b**.*

To a solution of **15** (53 mg, 0.2 mmol), EDCI (115.0 mg, 0.6 mmol), DMAP (1.2 mg, 0.01 mmol) and **17a** or **17b** (63 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added TEA (83 μL, 0.6 mmol)

at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield **20a** or **20b**.

*4.1.13.1 ((1aR,7aS,8S,10aS,10bS,E)-1a,8-Dimethyl-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,5-dimethoxyphenyl)acrylate (**20a**)*: white solid (yield: 77%), mp 83-85 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 16.1 Hz, 1H, H-18), 7.01 (d, *J* = 2.9 Hz, 1H, Ar-H), 6.90 (dd, *J* = 9.0, 2.9 Hz, 1H, Ar-H), 6.83 (d, *J* = 9.0 Hz, 1H, Ar-H), 6.49 (d, *J* = 16.1 Hz, 1H, H-17), 5.67 (t, *J* = 8.2 Hz, 1H, H-1), 4.77 (d, *J* = 12.5 Hz, 1H, H-14), 4.52 (d, *J* = 12.6 Hz, 1H, H-14), 3.87 – 3.79 (m, 4H, H-6, OCH_3), 3.76 (s, 3H, OCH_3), 2.76 (d, *J* = 9.4 Hz, 1H, H-5), 2.52 – 2.41 (m, 1H, H-7), 2.35 – 2.08 (m, 6H, C$\underline{H}_2$), 2.06 – 1.96 (m, 1H, C$\underline{H}$), 1.63 – 1.55 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.27 (d, *J* = 6.9 Hz, 3H, H-13), 1.06 (t, *J* = 13.1 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8(C-12), 166.9(C-16), 153.3(Ar-C), 152.8(Ar-C), 140.6(C-18), 135.2(C-10), 129.8(C-1), 123.4(C-17), 118.0(Ar-C), 117.2(Ar-C), 113.3(Ar-C), 112.3(Ar-C), 81.0(C-6), 66.1(C-14), 63.3(C-5), 59.7(C-4), 55.9(Ar-O$\underline{C}H_3$), 55.6(Ar-O$\underline{C}H_3$), 46.1(C-11), 41.3(C-7), 36.7(C-3), 26.6(C-8), 24.4(C-9), 23.6(C-2), 17.8(C-15), 13.0(C-13). HRMS (ESI) calcd for $C_{26}H_{32}NaO_7$ $[M+Na]^+$ 479.2040, found 479.2046.

*4.1.13.2 ((1aR,7aS,8S,10aS,10bS,E)-1a,8-Dimethyl-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl-(E)-3-(2,6-dimethoxyphenyl)acrylate (**20b**):* white solid (yield: 84%), mp 79-81 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 16.3 Hz, 1H, H-18), 7.31 – 7.21 (m, 1H, Ar-H), 6.87 (d, *J* = 16.3 Hz, 1H, H-18), 6.54 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.68 (t, *J* = 8.0 Hz, 1H, H-1), 4.76 (d, *J* = 12.5 Hz, 1H, H-

14), 4.51 (d, *J* = 12.5 Hz, 1H, H-14), 3.91 – 3.79 (m, 7H, H-6, OC<u>H</u>$_3$), 2.79 (d, *J* = 9.3 Hz, 1H, H-5), 2.50 – 2.40 (m, 1H, C<u>H</u>$_2$, C<u>H</u>), 2.36 – 2.01 (m, 7H, C<u>H</u>$_2$), 1.62 – 1.50 (m, 4H, H-15, C<u>H</u>), 1.27 (d, *J* = 6.7 Hz, 3H, H-13), 1.07 (t, *J* = 13.0 Hz, 1H, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0(C-12), 168.3(C-16), 160.2(Ar-C), 136.4(C-18), 135.6(C-10), 131.7(Ar-C), 130.0(C-1), 119.7(C-17), 111.9(Ar-C), 103.7(Ar-C), 81.2(C-6), 66.2(C-14), 63.5(C-5), 59.9(C-4), 55.8(Ar-OC<u>H</u>$_3$), 46.3(C-11), 41.6(C-7), 36.9(C-3), 26.9(C-8), 24.8(C-9), 23.8(C-2), 18.0(C-15), 13.1(C-15). HRMS (ESI) calcd for $C_{26}H_{32}NaO_7$ $[M+Na]^+$ 479.2040, found 479.2045..

*4.1.14 General procedure for the synthesis of compounds **21a** and **21b**.*

The acid **17a** or **17b** (400 mg, 1.92 mmol) and 10% Pd/C was dissolved in MeOH (20 mL) and the mixture was stirred under hydrogen atmosphere at 20 °C untill completion of reaction (TLC). The resulting mixture was filtered through a short pad of silica gel, concentrated under reduced pressure to give the crude acid **18a** or **18b** was directed to next step. To a solution of crude acid **18a** or **18b** (167 mg, 0.79 mmol), compound **2** (140 mg, 0.53 mmol), EDCI (153 mg, 0.79 mmol) and DMAP (0.6 mg, 0.053 mmol) was in 5 mL dry CH_2Cl_2 was added TEA (110 μL, 0.79 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield **21a** or **21b**.

*4.1.14.1 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl 3-(2,5-dimethoxyphenyl)propanoate (**21a**)*: white solid (yield: 85%), mp 109-111 □. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.66 (m, 3H, Ar-H), 6.20 (d, *J* = 3.5 Hz, 1H, H-13), 5.61 (t, *J* = 8.0 Hz,

1H, H-1), 5.50 (d, *J* = 3.5 Hz, 1H, H-13), 4.62 (d, *J* = 12.4 Hz, 1H, H-14), 4.40 (d, *J* = 12.4 Hz, 1H, H-14), 3.80 (t, *J* = 9.3 Hz, 1H, H-6), 3.75 (s, 3H, OC$\underline{H}_3$), 3.71 (s, 3H, OC$\underline{H}_3$), 2.89 (m, 2H, H-18), 2.84 – 2.79 (m, 1H, H-7), 2.77 (d, *J* = 9.4 Hz, 1H, H-5), 2.60 (t, *J* = 7.5 Hz, 2H, H-17), 2.42 – 2.08 (m, 6H, C$\underline{H}_2$), 1.59 (td, *J* = 12.1, 3.1 Hz, 1H, C$\underline{H}_2$), 1.51 (s, 3H, H-15), 1.05 (t, *J* = 12.5 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.8(C-12), 169.3(C-16), 153.1(Ar-C), 151.5(Ar-C), 138.6(C-11), 134.8(C-10), 130.5(C-1), 129.5(Ar-C), 120.1(C-13), 116.3(Ar-C), 111.2(Ar-C), 110.9(Ar-C), 80.9(C-2), 66.6(C-14), 63.1(C-5), 59.8(C-4), 55.6(Ar-O$\underline{C}H_3$), 55.5(Ar-O$\underline{C}H_3$), 42.5(C-7), 36.4(C-3), 33.9(C-17), 26.1(C-8), 25.6(C-9), 24.4(C-18), 23.7(C-2), 17.9(C-15). HRMS (ESI) calcd for $C_{26}H_{36}NO_7$ $[M+NH_4]^+$ 474.2486, found 474.2484.

*4.1.14.2 ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-yl)methyl 3-(2,6-dimethoxyphenyl)propanoate (**21b**)*: white solid (yield: 83%), mp 124-126 □. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.13 (t, *J* = 8.3 Hz, 1H, Ar-H), 6.51 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.21 (d, *J* = 3.5 Hz, 1H, H-13), 5.64 (t, *J* = 8.0 Hz, 1H, H-1), 5.52 (d, *J* = 3.1 Hz, 1H, H-13), 4.61 (d, *J* = 12.4 Hz, 1H, H-14), 4.46 (d, *J* = 12.4 Hz, 1H, H-14), 3.82 (t, *J* = 9.4 Hz, 1H, H-6), 3.79 (s, 6H, OC$\underline{H}_3$), 3.02 – 2.91 (m, 2H, H-18), 2.91 – 2.83 (m, 1H, H-7), 2.81 (d, *J* = 9.4 Hz, 1H, H-5), 2.51 – 2.44 (m, 2H, H-17), 2.44 – 2.11 (m, 6H, C$\underline{H}_2$), 1.68 – 1.57 (m, 1H, C$\underline{H}_2$), 1.53 (s, 3H, H-15), 1.09 (t, J = 12.4 Hz, 1H, C$\underline{H}_2$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.5(C-12), 169.5(C-16), 158.3(Ar-C), 138.9(C-11), 135.1(C-10), 130.7(C-1), 127.5(Ar-C), 120.3(C-13), 116.4(Ar-C), 103.6(Ar-C), 81.1(C-6), 66.9(C-14), 63.3(C-5), 60.0(C-4), 55.7(Ar-O$\underline{C}H_3$), 42.7(C-7), 36.7(C-3), 33.5(C-17), 26.0(C-8), 24.8(C-9), 23.9(C-2), 18.8(C-18), 18.1(C-15). HRMS (ESI) calcd for $C_{26}H_{32}NaO_7$ $[M+Na]^+$ 479.2040, found 479.2045.

4.2 Biological assay

4.2.1. Cell culture

Human breast cancer cell lines MDA-MB-231, SUM-159, MCF-7, BcaP-37 and 4T1 triple negative breast cancer cells of mouse were purchased from ATCC. These cancer cells were cultured in 1640 medium supplement with 10% FBS under a 5% CO_2 humidified atmosphere at 37 °C.

4.2.2. MTT assay

As to MTT assay, cells were seeded with a density of at 5000 cells/200 μL/well into 96 well plate. After 8-12 hours, the compounds were diluted to a series concentration and added into the 96 well plate. After incubated for 72 hours, 20 μL thiazolyl blue tetrazolium bromide (MTT, 5 mg/mL) was added and incubated at 37 °C for additional 4 hour. Then supernatant was discarded and 200 μL DMSO was added to dissolve the precipitate. After 15 mins shaken at room temperature the absorbance was measured at 570 nm using a micro-plate reader (synergy H4, BioTek, USA). IC_{50} values were calculated using GraphPad Prism 5 software.

4.2.3. Cell apoptosis assay

SUM-159 cells were seeded into 24-well plate with the density at 1×10^5 cells/mL/well. Then 110μL compound **7d** at the concentration of 2 μM and 5 μM after diluted with culture medium were added and incubated for 48 hours. After that the cells were digested and collected by centrifugation. Following that the supernatant was discarded and the cells were resuspended with 100 μL of 1× binding buffer. The cells were stained with 5 μL of Annexin V-APC and 5 μL PI at room temperature for 15 min in dark. Then the cells were analyzed within one hour by flow cytometry (BD LSRII flow cytometer (BD Biosciences, New Jersey, America).

4.2.4. Cell cycle assay

SUM-159 cells were seeded into 24-well plate with the density at 1×10^5 cells/mL/well. Then compound **7d** at the concentration of 0.5 μM were added and incubated for 48 hours. After collected, the cells were immobilized with 75% ethanol on ice for 1 hours. The cells were washed and resuspended with PBS buffer supplement with 100 μL RNase A (100 μg/mL) and PI. After incubation for 30 mins on ice, the cells were analyzed by flow cytometry (BD LSRII flow cytometer (BD Biosciences, New Jersey, America).

4.2.5. Western blot assay

SUM-159 cells in logarithmic growth period were plated into 6-well plate with the density at 1×10^5 cells/mL/well. Then compound **7d** at the concentration of 0.1 μM and 0.2 μM were added and incubated for 48 hours. After that the cells were collected and resuspended with cell lysate buffer for 30 mins on ice. The cell lysates (50 μg) were separated by 12% tris-acrylamide gel electrophoresis and were transferred onto PVDF membrane. Following that the membrane was blocked in 5% skim milk for 1 hour at room temperature, and subsequently was incubated with primary antibodies at 4 °C overnight on rotary shaker. After washing the membrane for 5 times, the peroxidase-conjugated goat anti-mouse IgG or goat anti-rabbit IgG were diluted with 1:10000 and incubated with the membrane for 2 hours at room temperature. Then the membrane was washed for 5 times and developed with ECL reagent (Thermo Scientific, Rockford, America).

*4.3 Reaction of **7d**, **20b**, and **21b** with GSH*

The compounds **7d**, **20b**, **21b** (15 mg) were incubated with an excess of GSH (25–30 mg) in deuterated phosphate buffer at pH 7.4 (0.05 mL) and DMSO-d6 (0.50 mL) at 37 °C. The reaction

was monitored by the change of representative hydrogen signals with ^{1}H NMR analysis, and the adduct products were confirmed with the HRMS. The reactivities of the covalent warheads could be initially classified based on the integration change of the representative proton NMR.

SUPPORTING INFORMATION

Copies of the NMR spectra of all new compounds, copies of ^{1}H NMR and HRMS for checking reaction of PTL derivatives with GSH.

NOTES

The authors declare no competing financial interest.

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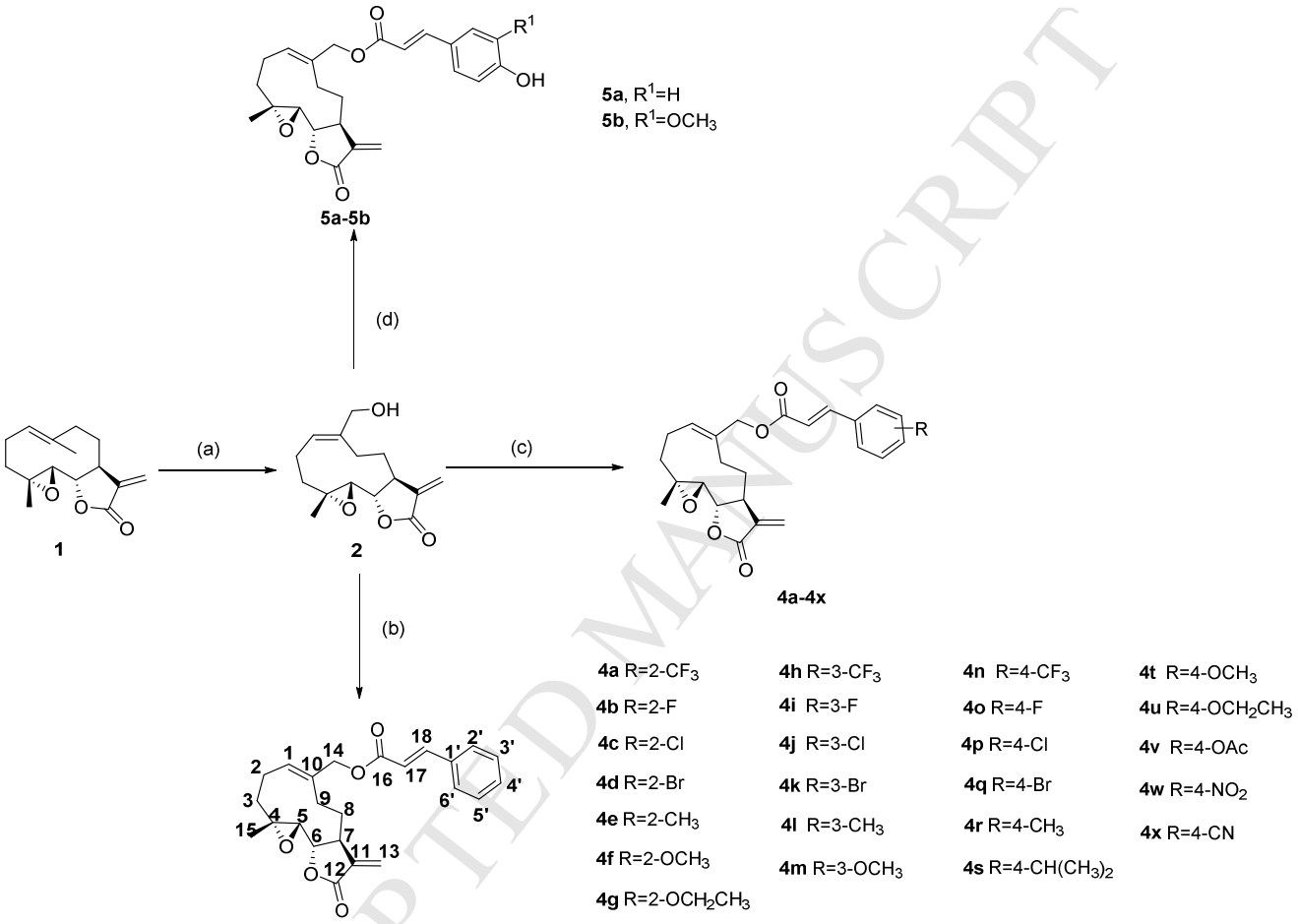
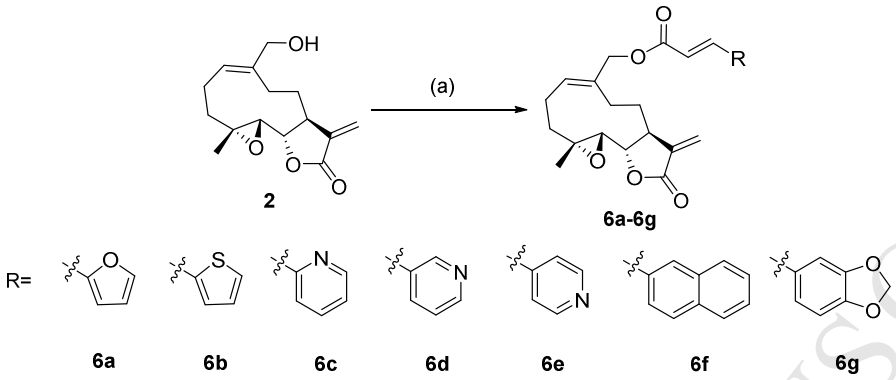
Scheme 1. Synthesis of Analogues 3, 4a–4x and 5a–5b.



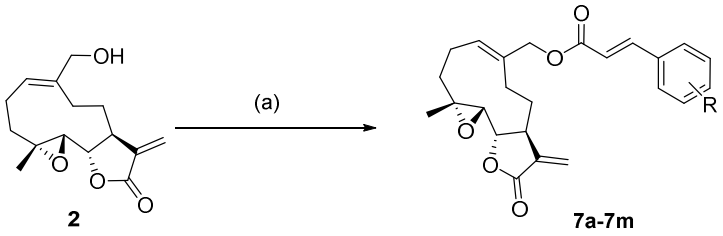
Reagents and conditions: (a) SeO_2, *t*-BuOOH, CH_2Cl_2, rt, overnight, 72%; (b) Cinnamic acid, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 86%; (c) Corresponding substituted cinnamic acid, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 53%–98%; (d) Coumaric acid for **5a** or ferulic acid for **5b**, DIAD, PPh_3, rt, 8 h, THF, 76% yield for **5a**, 55% yield for **5b**.

Scheme 2. Synthesis of Analogues 6a–6g.



Reagents and conditions: (a) For **6a**–**6b**, **6f**–**6g**: EDCI, TEA, DMAP, corresponding carboxylic acid, CH_2Cl_2, 0 ºC to rt, 8 h, 82%–95% yield; For **6c**–**6e**: corresponding carboxylic acid, oxalyl chloride, DMF, CH_2Cl_2 , 0 °C, 1.5 h, converted acids to corresponding acyl chlorides; acyl chloride, compound **2**, CH_2Cl_2, rt, 2 h, 67%–77% yield for **6c**–**6e**.

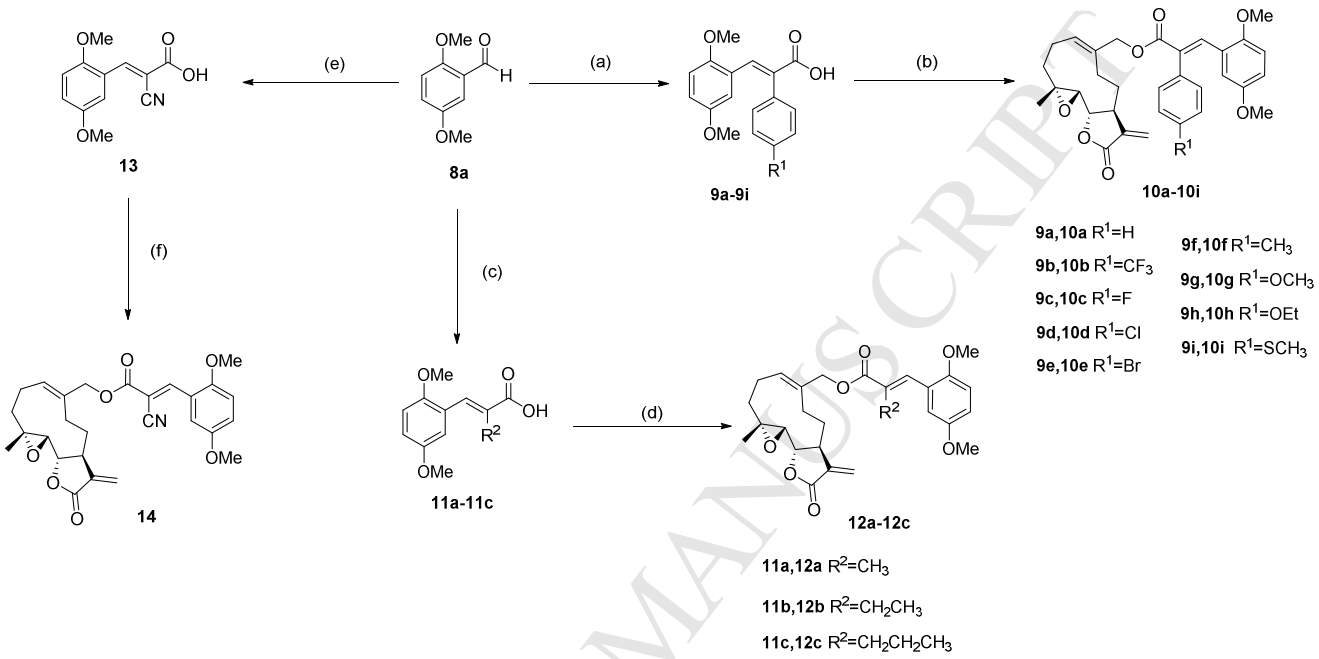
Scheme 3. Synthesis of Analogues 7a–7g.



7a R=2,3-OCH_3
7b R=2,4-OCH_3
7c R=2,5-OCH_3
7d R=2,6-OCH_3
7e R=3,4-OCH_3
7f R=3,5-OCH_3
7g R=2,3,4-OCH_3
7h R=2,4,5-OCH_3
7i R=2,4,6-OCH_3
7j **R=**3,4,5-OCH_3
7k R=2,6-F
7l R=2,6-Cl
7m R=2,6-Br

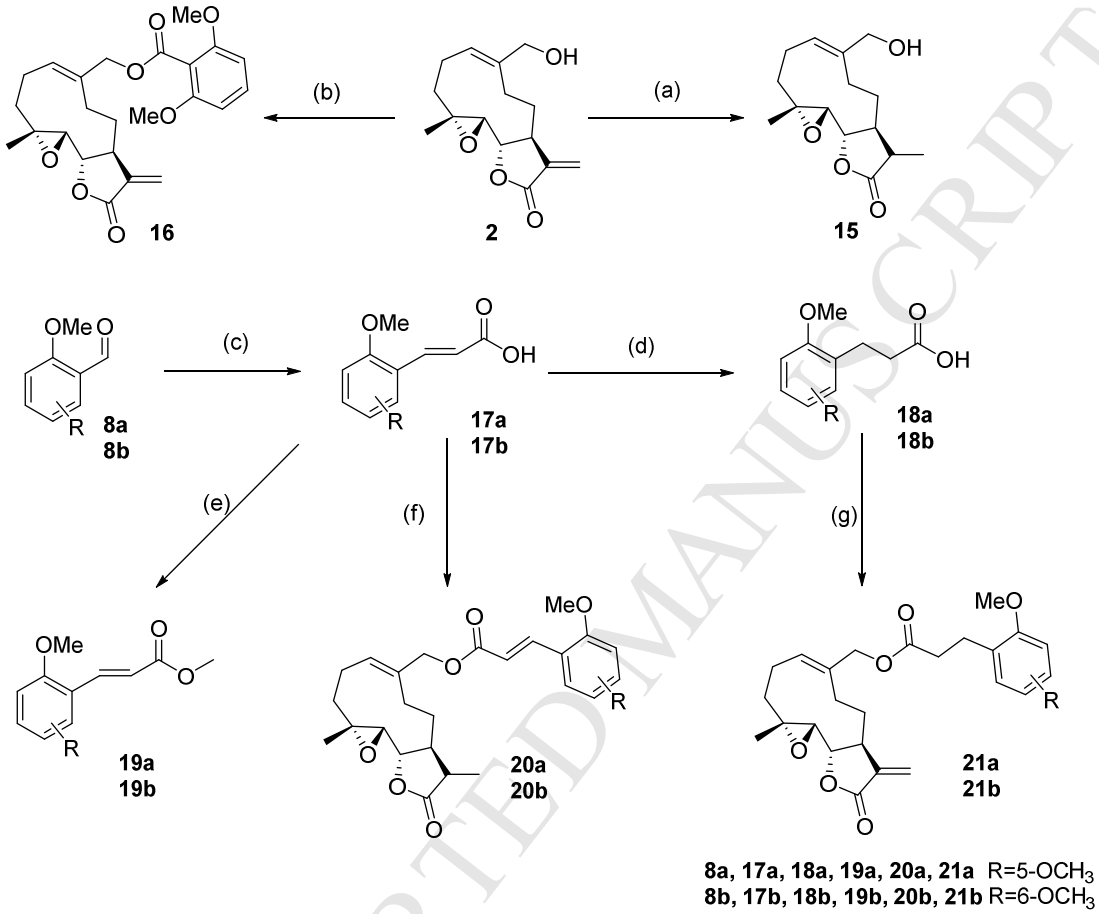
Reagents and conditions: (a) EDCI, TEA, DMAP, corresponding carboxylic acid, CH_2Cl_2, 0 ºC to rt, 8 h, 56%–94% yield for **7a**–**7m**.

Scheme 4. Synthesis of Analogues 10a–10i, 12a–12c and 14.



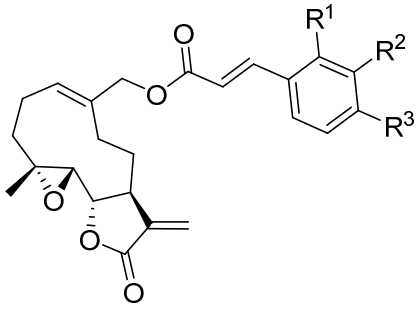
Reagents and conditions: (a) Corresponding substituted phenyl acetic acid, Ac_2O, TEA, refluxed, 4–9 h, directly used for next step; (b) Compound **2**, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 65%–93% yield for **10a**–**10i**; (c) Corresponding substituted malonic acid, pyridine and piperidine, refluxed overnight, directly used for next step; (d) Compound **2**, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 54%–95% yield for **12a**–**12c**; (e) Cyanoacetic acid, pyridine and piperidine, refluxed overnight, directly used for next step; (f) Compound **2**, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 83%.

Scheme 5. Synthesis of Analogues 16, 19a–19b, 20a–20b and 21a–21b.



Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 4 h, 77%; (b) 2,6-Dimethoxybenzoic acid, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 83%; (c) Malonic acid, pyridine and piperidine, refluxed overnight, 67% yield for **17a**, 57% yield for **17b**; (d) Pd/C, H_2, MeOH, 20 °C, 2–6 h; (e) Thionyl chloride, MeOH, CH_2Cl_2, 75 °C for 2 h, 75%–81%; (f) Compound **15**, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 77%–84%; (g) Compound **2**, EDCI, TEA, DMAP, CH_2Cl_2, 0 ºC to rt, 8 h, 83%–84%.

Table 1. Antiproliferative efficacy of parthenolide derivatives 3, 4a–4x and 5a–5b in human breast cancer cell line MDA-MB-231.



3, 4a-4x, 5a-5b

Compound	R^1	R^2	R^3	$IC_{50}{}^a$(μM)
3	H	H	H	1.35±0.19
4a	CF_3	H	H	0.74±0.39
4b	F	H	H	1.80±0.11
4c	Cl	H	H	1.42±0.21
4d	Br	H	H	1.33±0.36
4e	Me	H	H	1.79±0.26
4f	OMe	H	H	0.46±0.22
4g	OEt	H	H	0.34±0.05
4h	H	CF_3	H	0.83±0.43
4i	H	F	H	1.73±0.52

4j	H	Cl	H	1.78±0.57
4k	H	Br	H	1.64±0.11
4l	H	Me	H	1.08±0.59
4m	H	OMe	H	1.84±0.21
4n	H	H	CF_3	2.52±0.47
4o	H	H	F	1.32±0.02
4p	H	H	Cl	1.22±0.45
4q	H	H	Br	1.02±0.81
4r	H	H	Me	2.27±0.95
4s	H	H	i-Pr	1.33±1.05
4t	H	H	OMe	1.73±0.63
4u	H	H	OEt	1.58±0.56
4v	H	H	OAc	1.15±0.30
4w	H	H	NO_2	1.93±0.20
4x	H	H	CN	1.80±0.30
5a	H	H	OH	1.89±0.69

5b	H	OMe	OH	2.01±0.54
PTL[b]	-			3.48±1.19
MMB[c]	-			5.59±1.39
ADR[d]	-			0.80±0.09

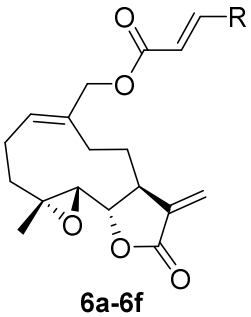
[a]All values are the mean of three independent experiments.

[b]PTL, parthenolide;

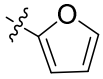
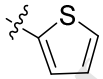
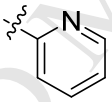
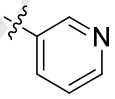
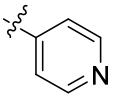
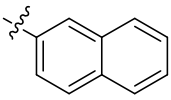
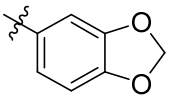
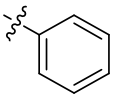
[c]MMB, melampomagnolide B;

[d]ADR, Adriamycin.

Table 2. Antiproliferative Efficacy of 6a–6f in Human Breast Cancer Cell Lines MDA-MB-231.



6a-6f

Compounds	R	$IC_{50}{}^{a}$(μM)
6a		2.25±0.14
6b		1.80±0.099
6c		2.29±1.00
6d		3.27±0.37
6e		2.79±0.54
6f		1.48±0.32
6g		1.80±0.71
3		1.35±0.19

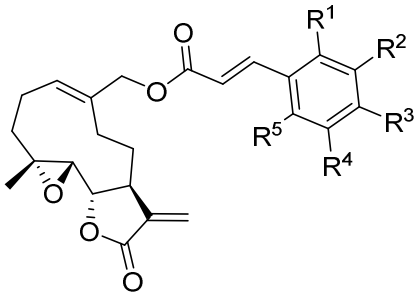
PTL[b]	-	3.48±1.19
ADR[c]	-	0.80±0.09

[a]All values are the mean of three independent experiments.

[b]PTL, parthenolide;

[c]ADR, Adriamycin.

Table 3. Antiproliferative Efficacy of compounds 7a–7m in MDA-MB-231 cell line.



7a-7m

Compounds	R^1	R^2	R^3	R^4	R^5	$IC_{50}{}^{a}$(μM)
3	H	H	H	H	H	1.35±0.19
7a	OMe	OMe	H	H	H	1.74±0.41
7b	OMe	H	OMe	H	H	0.55±0.31
7c	OMe	H	H	OMe	H	0.26±0.04
7d	OMe	H	H	H	OMe	0.25±0.02
7e	H	OMe	OMe	H	H	1.95±0.11
7f	H	OMe	H	OMe	H	2.02±0.35
7g	OMe	OMe	OMe	H	H	1.77±0.09
7h	OMe	H	OMe	OMe	H	1.02±0.45
7i	OMe	H	OMe	H	OMe	1.09±0.21

7j	H	OMe	OMe	OMe	H	0.95±0.06
7k	F	H	H	H	F	1.59±0.23
7l	Cl	H	H	H	Cl	1.59±0.23
7m	Br	H	H	H	Br	1.50±0.22
PTL[b]	-					3.48±1.19
MMB[c]	-					5.59±1.39
ADR[d]	-					0.80±0.09

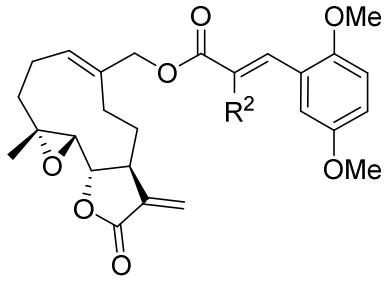
[a]All values are the mean of three independent experiments.

[b]PTL, parthenolide;

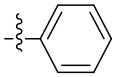
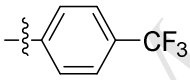
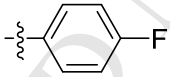
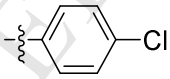
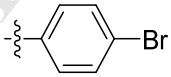
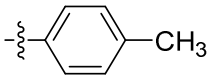
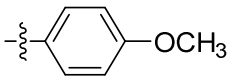
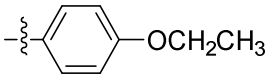
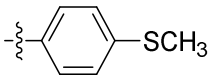
[c]MMB, melampomagnolide B;

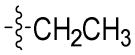
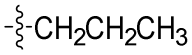
[d]ADR, Adriamycin.

Table 4. Antiproliferative Efficacy of 10a–10i, 12a–12c and 14 in Human Breast Cancer Cell Line MDA-MB-231.



10a-10i, 12a-12c, 14

Compounds	R^2	$IC_{50}{}^{a}$(μM)
10a		2.01±0.21
10b		1.98±0.34
10c		1.96±0.22
10d		2.02±0.18
10e		2.01±0.56
10f		2.95±1.19
10g		2.51±1.22
10h		1.87±0.81
10i		1.87±0.15
12a		1.76±0.20

12b		2.25±0.14
12c		7.53±2.91
14		2.35±1.27
7c		0.26±0.04
PTL[b]	-	3.48±1.19
MMB[c]	-	5.59±1.39
ADR[d]	-	0.80±0.09

[a]All values are the mean of three independent experiments.

[b]PTL, parthenolide;

[c]MMB, melampomagnolide B;

[d]ADR, Adriamycin.

Table 5. Antiproliferative efficacy of 16, 17b, 19a–b, 20a–b, 21a–b in human breast cancer cell line MDA-MB-231.

Compounds	IC_{50}[a] (μM)
16	3.55±0.03
17b	>50
19a	>50
19b	>20
20a	6.80±3.35
20b	7.60±1.70
21a	1.88±0.27
21b	2.30±0.53
MMB and **17b** (1:1)	3.92±0.77
7d	0.25±0.02
PTL[b]	3.48±1.19
MMB[c]	5.59±1.39
ADR[d]	0.80±0.09

[a]All values are the mean of three independent experiments.

[b]PTL, parthenolide;

[c]MMB, melampomagnolide B.

[d]ADR, Adriamycin.

Table 6. Inhibitory Effect of 4a, 4f, 4g, 4h, 7b–7d and 7j against Various Breast Cancer Cell Lines.

Compounds	IC_{50}[a](μM)				
	MDA-MB231[b]	SUM-159[c]	MCF-7[d]	Bcap-37[e]	4T1[f]
4a	0.74±0.39	0.85±0.028	2.01±0.20	1.89±0.97	1.16+0.42
4f	0.46±0.22	0.35±0.16	0.42±0.16	0.68±0.16	0.52+0.07
4g	0.34±0.049	0.21±0.007	0.29±0.014	0.42±0.33	0.18+0.01
4h	0.83±0.43	0.64±0.007	2.15±0.31	1.86±0.54	1.48±0.13
7b	0.55±0.31	0.80±0.11	0.89±0.22	1.15±0.028	1.41±0.05
7c	0.26±0.039	0.26±0.07	0.26±0.07	0.55±0.12	0.34±0.04
7d	0.25±0.20	0.20±0.05	0.23±0.12	0.27±0.11	0.22±0.01
7j	0.95±0.057	0.86±0.53	1.39±0.078	1.96±0.76	0.63±0.09
PTL[g]	3.48±1.19	3.06±0.94	2.68±0.83	4.63±1.07	4.09±0.03

[a]All values are the mean of three independent experiments. [b]MDA-MB-231, human triple-negative breast cancer cell line. [c]SUM159, human triple-negative breast cancer cell line. [d]MCF7, human breast cancer cell line. [e]Bcap37, human breast cancer cell line. [f]4T1, mouse triple-negative breast cancer cell line. [g]PTL, parthenolide.

Table 7. Toxicity of compound 7d against 3T3 cells.

Compound	IC_{50}[a](μM)		TI[d]
	4T1[b]	3T3[c]	
7d	0.22±0.01[e]	8.13±2.72	36.9
ADR[f]	0.80±0.09[g]	0.36±0.075	0.45

[a]All values are the mean of three independent experiments.

[b]4T1, mouse triple-negative breast cancer cell line.

[c]3T3, mouse embryonic fibroblasts cell line.

[d]TI, therapeutic index = IC_{50}(3T3)/IC_{50}(4T1).

[e]Data from Table 6.

[f]ADR, adriamycin, a clinically used drug, was used as a positive control.

[g]Data from Table 1.

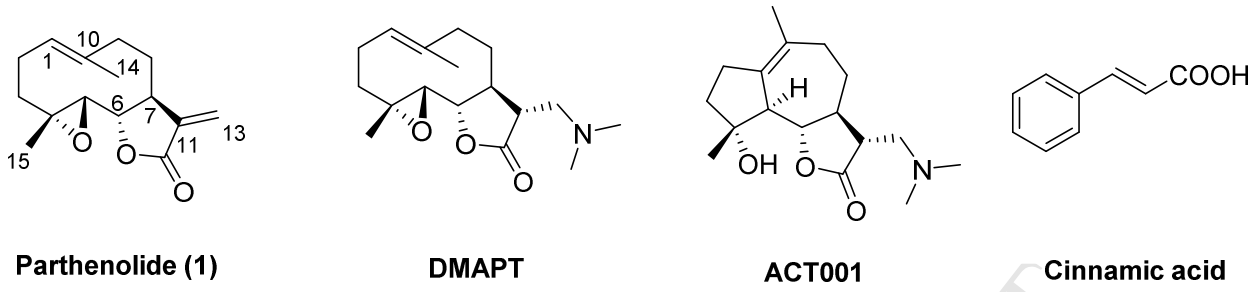


Figure 1. Structures of PTL (**1**), DMAPT, ACT001, and cinnamic acid.

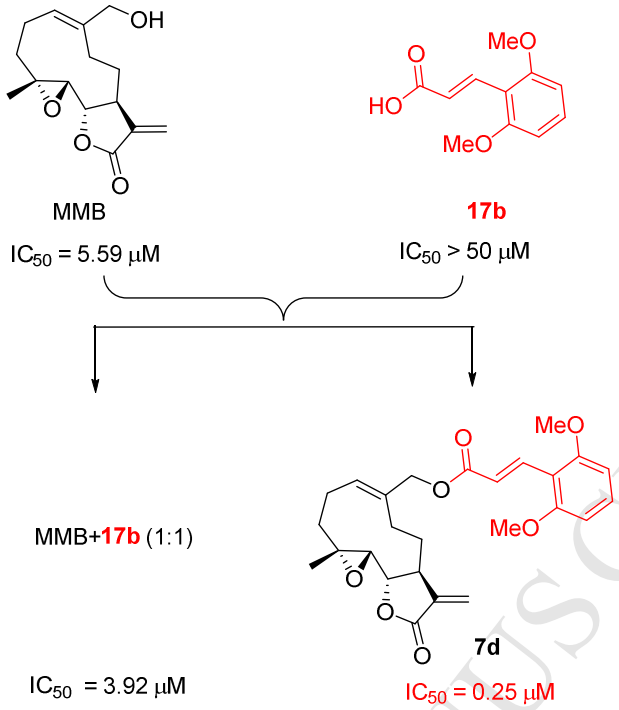


Figure 2. Comparison of anti-TNBC activity of **7d** with that of MMB, **17b**, and an equimolar mixture of MMB and **17b**.

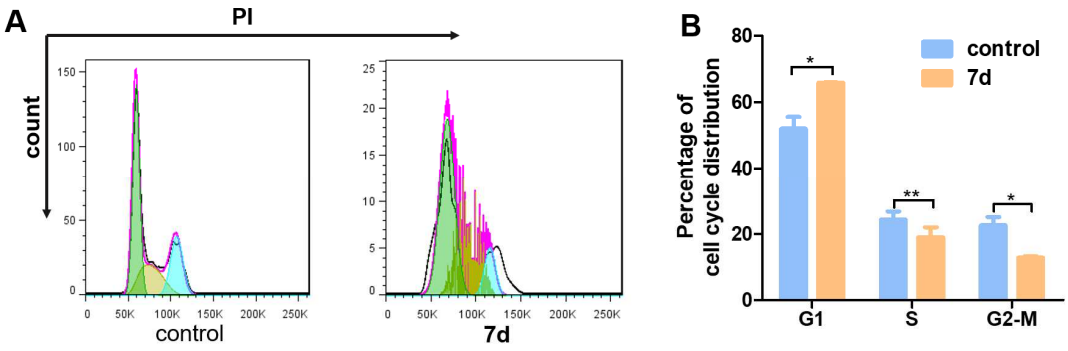


Figure 3. Compound **7d** induced G1 phase cell cycle arrest of SUM-159 cells. (A) The representative images of cell cycle distribution in the presence of compound **7d**. (B) The statistical results of cell cycle distribution of SUM-159 cells after treatment of compound **7d**.

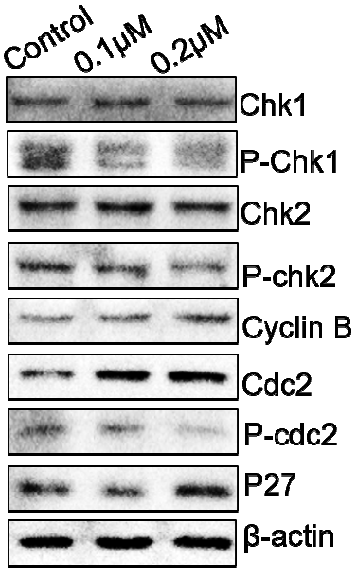


Figure 4. The change of cell cycle related proteins in SUM-159 cells after the treatment of compound **7d** at 0.1 μM and 0.2 μM by western blot assay.

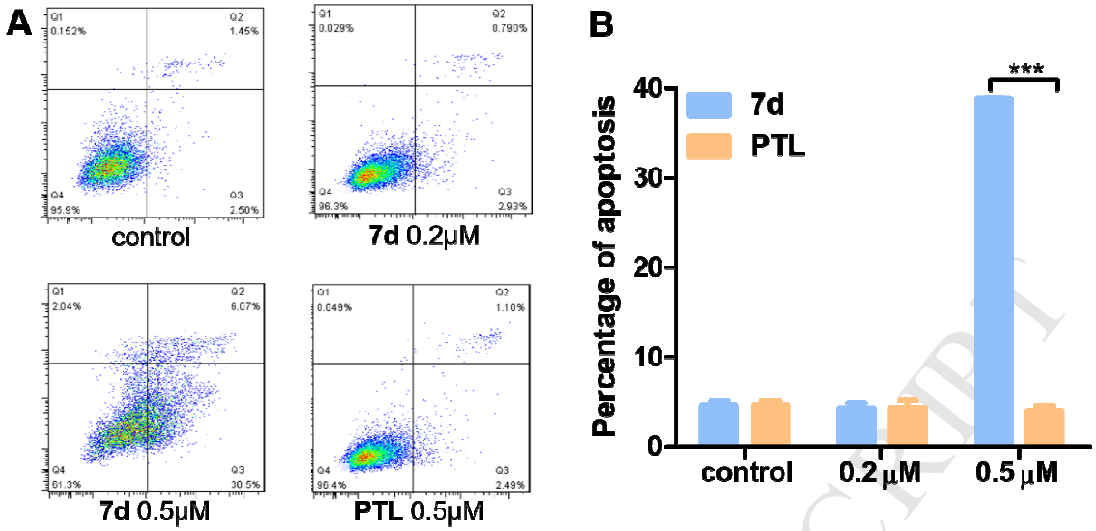


Figure 5. The percentage of cell apoptosis after the treatment of compound **7d** for 48 hours. (A) The representative images of cell apoptosis at 0.2 μM, 0.5 μM of compound **7d** and 0.5 μM of PTL. (B) The statistical results of cell apoptosis assays.

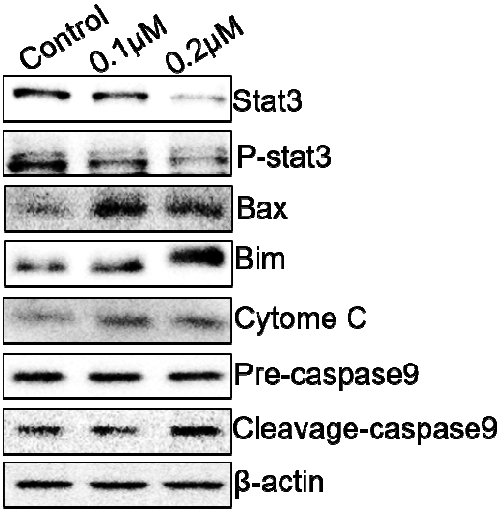
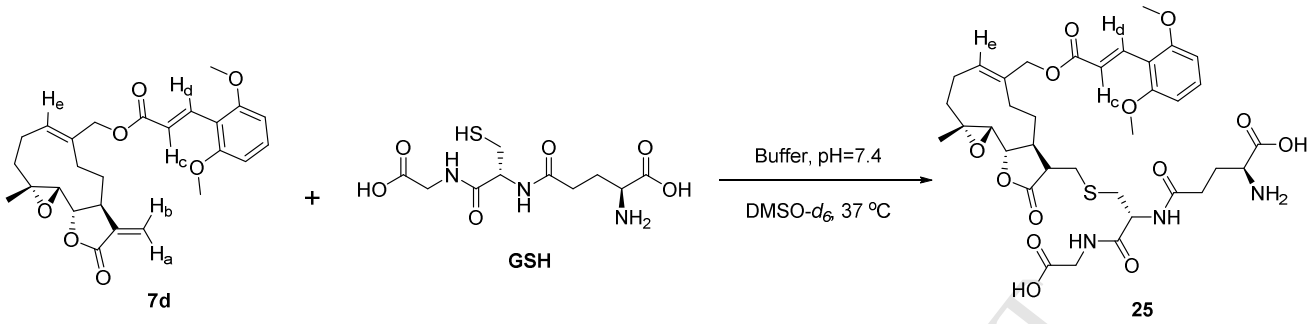


Figure 6. Western blot analysis of apoptosis related proteins of mitochondrial pathway after the treatment of compound **7d** for 48 hours at concentrations of 0.1 μM and 0.2 μM.



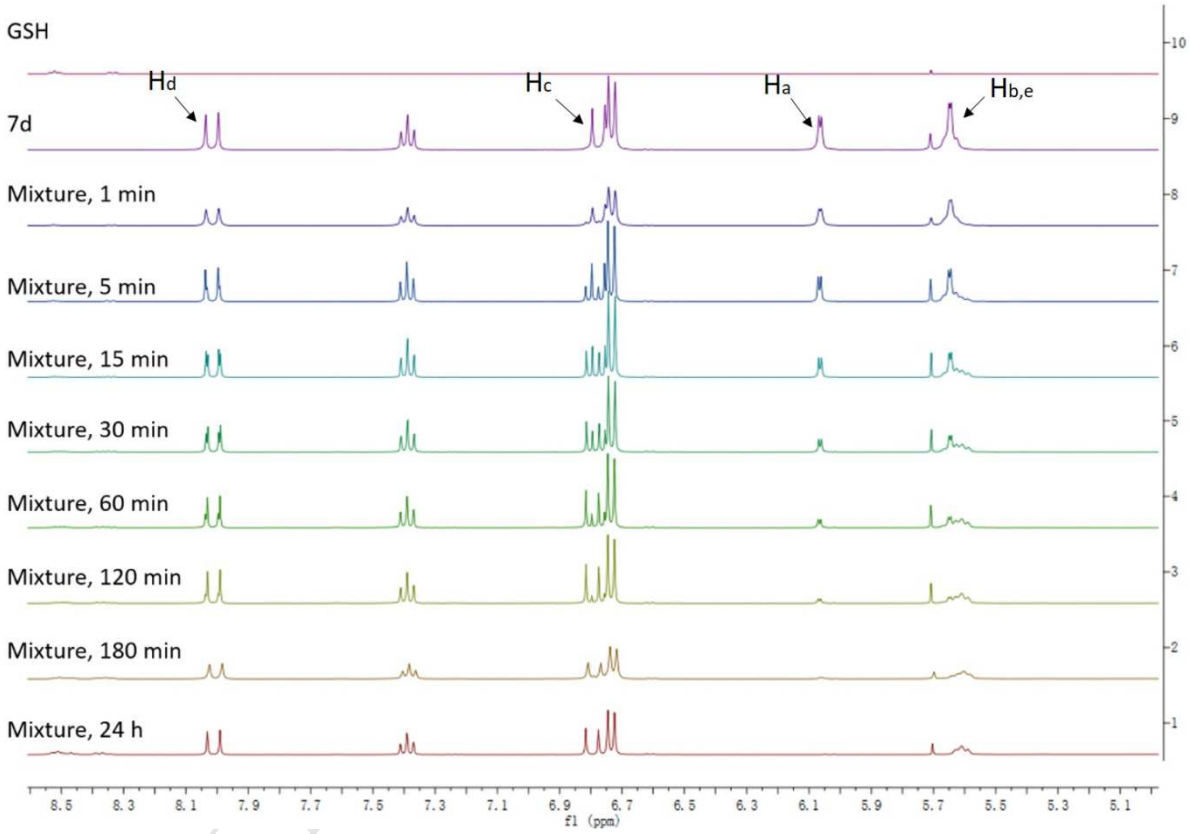
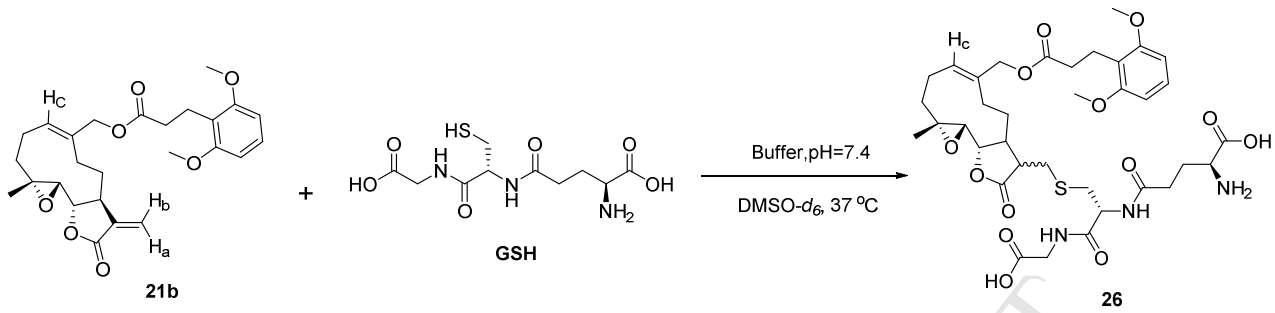


Figure 7. Reactivity of **7d** with GSH determined by ^{1}H NMR.



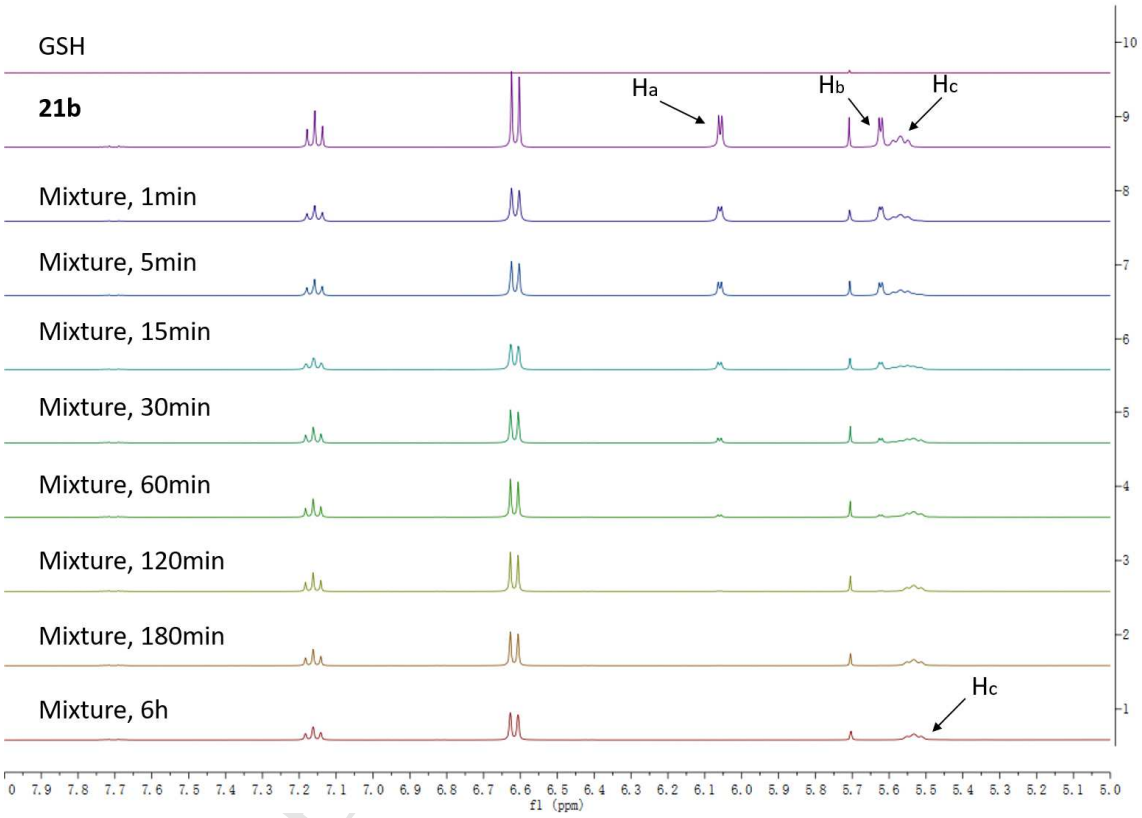
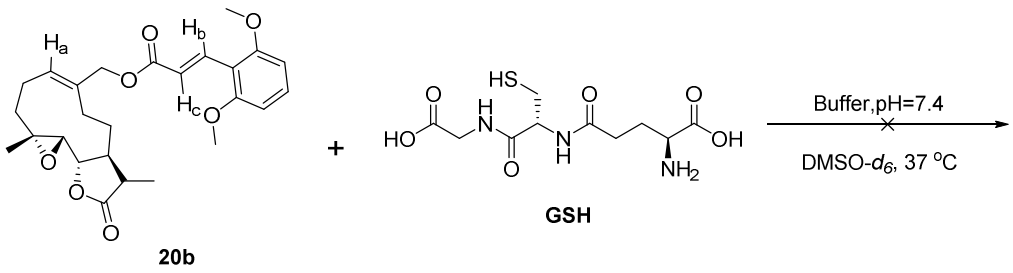


Figure 8. Reactivity of **21b** with GSH determined by ^{1}H NMR.



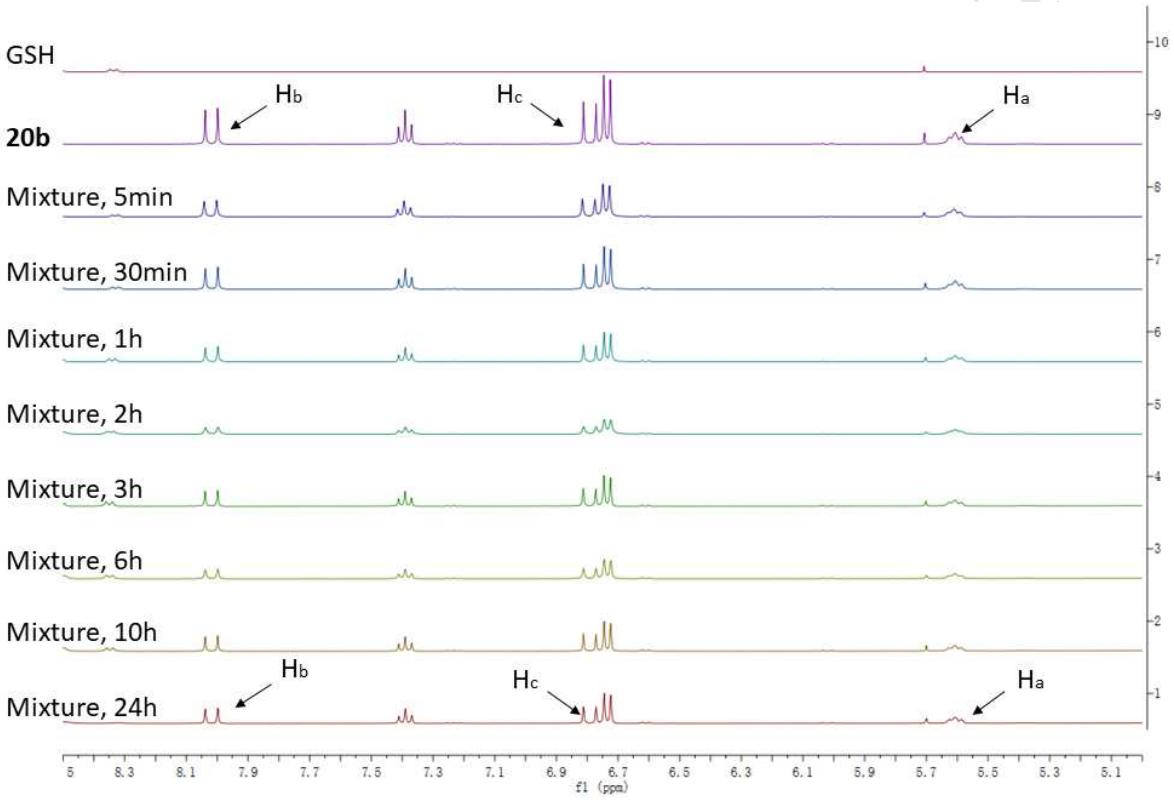


Figure 9. Reactivity of **20b** with GSH determined by ^{1}H NMR.

Highlights

- Seventy parthenolide derivatives were prepared.
- **7d** was 11.6- to 18.6-fold more active than parthenolide against five TNBC cells.
- Compound **7d** caused G1 phase arrest of SUM-159 cells.
- **7d** induced apoptosis of SUM-159 cells through mitochondria-mediated pathway.