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Site-Selective Synthesis of C-17 Ester Derivatives of Natural Andrographolide for Evaluation as a Potential Anticancer Agent

Gulshan Kumar, Sonia Thapa, Javeed Ahmad Tali, Davinder Singh, Bhupesh Kumar Sharma, Kamakshya Nath Panda, Shashank K. Singh,* and Ravi Shankar*

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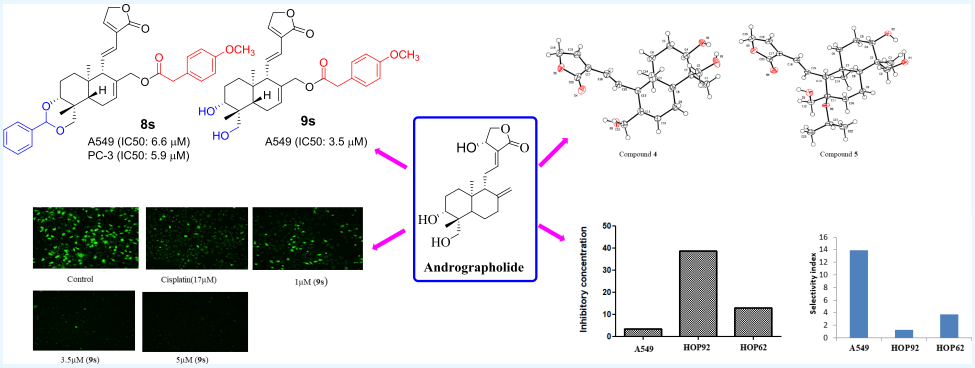

ABSTRACT: A library of 57 compounds of natural andrographolide was designed, synthesized, and screened for *in vitro* studies against four human cancer cell lines: A594, PC-3, MCF-7, and HCT-116. Most of the synthesized compounds displayed better cytotoxic profile against all tested cells compared to the parent andrographolide (**1**). The tested semisynthetic derivatives of andrographolide were found to be more sensitive toward lung carcinoma (A594) and prostate carcinoma (PC-3) cell lines. Among the synthesized compounds, the C-17 *p*-methoxy phenyl ester analog **8s** inhibited cell proliferation effectively in A549 (IC_{50}: 6.6 μM) and PC-3 (IC_{50}: 5.9 μM) cell variants, and compound **9s** exhibited the most potent activity against the A594 cell line, with an IC_{50} value of 3.5 μM. Further anticancer mechanistic investigation demonstrated that compound **9s** displayed nuclear morphological changes and increased reactive oxygen species (ROS) with disturbed mitochondrial membrane potential (MMP) that can lead to apoptosis. To know the exact structure confirmation of intermediate compounds **4** and **5**, single X-ray crystallography was performed, which supported the complete reaction design of this work.

1. INTRODUCTION

Natural products have been used extensively as traditional medicines for the treatment of various diseases because of their privileged structural diversity.[1,2] Andrographolide (**1**), one of the bicyclic labdane diterpenoids mainly isolated from the leaves of *Andrographis paniculata* (AP) Nees (family: *Acanthaceae*),[3] is also regarded as a significant natural product having multiple pharmacological properties. The synthetically modified andrographolide (**1**) derivatives were also reported for promising biological activities[4] such as antibacterial,[5] antimicrobial,[6,7] antihepatotoxic,[8,9] anti-HIV,[10,11] cardiovascular effects,[12] anticancer,[13−15] anti-inflammatory,[16−19] antimalarial,[20] antiviral,[20−22] antituberculosis,[23,24] antidiabetic,[25−29] and antioxidant.[30,31] Many anticancer mechanisms have been accepted for andrographolide (**1**) and its derivatives, including cytotoxicity against cancer cell, apoptosis method, and cell-cycle arrest mechanism. Our group is actively engaged in the development of biologically active natural products and synthetic scaffolds as part of a continuing effort to discover new and more effective anticancer agents.[4,32−35] Previous studies of the structure−activity relationships (SARs) of andrographolide have shown that esters on hydroxyl groups present at the C-3, C-19, and C-14 positions enhance pharmacological activities of andrographolide (**1**) relevant to its anticancer activity; *e.g.*, 14-acetylandrographolide,[36] 8,17-epoxy-3,19,14 ester andrographolide,[37] 14-cinnamoyl-8,17-epoxy-andrographolide (DRF-3188),[37,38] andrographolide-14α-*O*-iodoacetate,[39] 14-succinylandrographolide,[40] and 14α-*O*-(1,4-disubstituted-1,2,3-triazolyl) are biologically active synthetically modified ester derivatives of andrographolide (Figure 1).[41]

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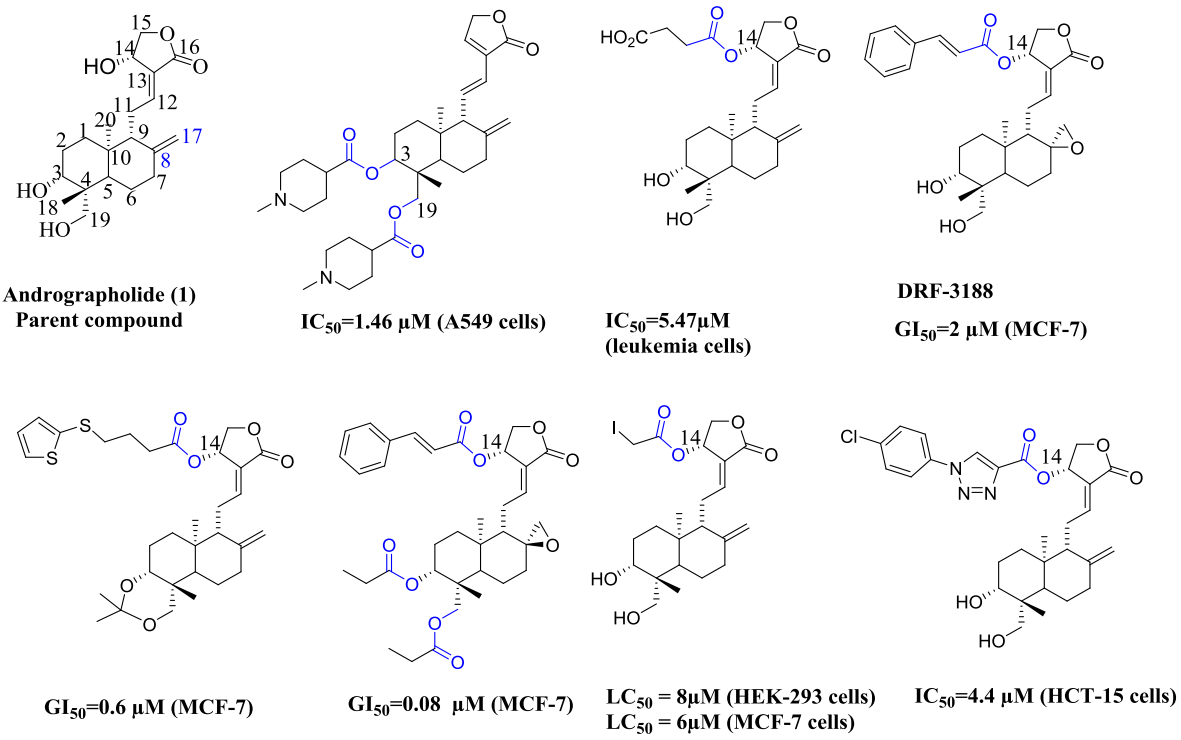


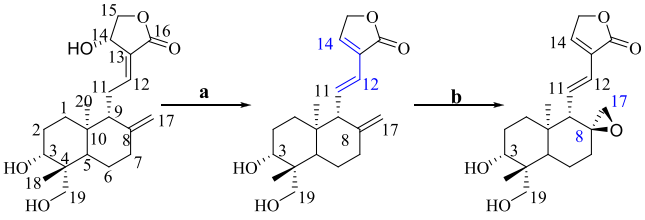
Figure 1. Ester-linked anticancer semisynthetic derivatives of andrographolide.

Realizing the fact that introduction of an ester group at positions C-3 and C-19 enhances the cytotoxicity of the parent molecule (**1**) and that no attempt has so far been made to link ester at the C-17 position of andrographolide (**1**), we therefore have decided to introduce an ester at the C-17 position (site selective) without affecting the other functionalities of andrographolide such as the α-alkylidene-γ-butyrolactone moiety and C-3, C-19 hydroxyl functional group. In this research work, we report site-selective synthesis of C-17 ester derivatives of andrographolide, and further, all synthesized compounds were *in vitro* tested for their ability to inhibit the growth of four human cancer cell lines: A594 (lung carcinoma), PC3 (prostate carcinoma), MCF-7 (breast carcinoma), and HCT-116 (colon carcinoma). Furthermore, biological assays such DAPI staining, the production of reactive oxygen species (ROS), and the determination of the mitochondrial membrane potential (MMP) of the most active compound, **9s**, have been carried out. Moreover, we disclose an in-depth analysis of structures of intermediate compounds **4** and **5**, which are the bases of current site-selective synthesis of C-17 ester derivatives of andrographolide (**1**).

2. RESULTS AND DISCUSSION

2.1. Chemistry. The andrographolide (**1**) used for experimental purpose was isolated from fresh leaf material of AP by using the reported literature.[42] The leaf material was air-dried for a day in the shade and dried in a hot-air oven below 60 °C, and the dried plant material was also powdered to a 40-mesh size for column chromatography. Thereafter, the methanol extract of AP was subjected to column chromatography, and the pure andrographolide (**1**) was isolated in 5% methanol/dichloromethane as a white powder. Thereafter, C_{17}-ester derivatives of andrographolide (**8a−y** and **9a−y**) were synthesized by first converting andrographolide (**1**) into 14-deoxy-11,12-didehydroandrographolide (**2**, 14-DDA) using the Al_2O_3 in pyridine at a reflux temperature,[43] resulting in the formation of **2** by dehydration at 14-OH, which showed significant peaks at δ 7.18 ppm for H-14 and δ 6.87 ppm for H-11 in ^{1}H NMR. Compound **2** was further treated with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane (DCM) at room temperature[43] to form 8-epoxy-14-deoxy-11,12-didehydroandrographolide (**3**), which was clearly confirmed by the ^{1}H NMR spectra; *e.g.*, the proton at $C_{8,17}$ in compound **2**, *viz.*, δ 4.77 and δ 4.52 ppm, shifted to δ 2.80 and δ 2.57 ppm in compound **3**, predicting the formation of C-8 epoxide in **3** (Scheme 1).

Scheme 1. Synthesis of C-8-Epoxide[a]



[a]Reagents and conditions: (a) Al_2O_3e, reflux, 24 h, 76%; (b) m-CPBA, DCM, 2 h, 92%.

Further, our target was opening of the C-8 epoxide of compound **3** to synthesize C-17 ester derivatives for biological screening. Therefore, we exploited molecule **3** with different acidic conditions in different solvents. We first examined compound **3** with Lewis acid like BF_3OEt_2 and $AlCl_3$ for epoxide opening, but unfortunately, we did not observe any desired products (entries 1 and 2). Afterward, we changed the acid source with H_2SO_4 (0.1 equiv) in DCM at room temperature and obtained compound **4** with 35% yield (entry

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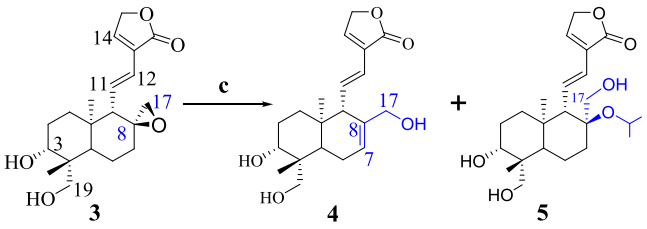
3). Compound **4** was considered as a desired compound as it contains a free allylic alcohol at the C-17 position, and hence, there can be chances for ester synthesis. Further, to increase the yield of desired **4**, we screened H_2SO_4 (0.1 equiv), an acid source, with different solvent systems, *viz.*, H_2O, tetrahydrofuran (THF), and isopropyl alcohol (IPA) (entries 4−6). Among them, IPA was found to be a more effective solvent in combination with H_2SO_4 (0.1 equiv), providing two products, **4** and **5**, in 45 and 5% yield (entry 6), whereas the remaining solvents were ineffective for the reaction (**4**; 30−38%, entries 4 and 5). Moreover, when increasing or decreasing the equivalents of the acid source, no major improvement has been observed in the yield (**4**; 25−40%) of the desired compound (entries 7−9). Later on, we also examined the opening of epoxide with other acids like camphorsulfonic acid (CSA), HNO_3, CH_3COOH, and trifluoroacetic acid (TFA) (entries 10−16). From all these observations, camphorsulfonic acid (CSA, 1.0 equiv) was found to be an effective acid for the epoxide opening in combination with IPA as solvent, yielding compounds **4** (70%) and **5** (10% yield), respectively (Table 1). The reaction of **3** with acid was also carried out above the

Table 1. Optimization Method for the Synthesis of Compounds 4 and 5 by Epoxide Opening[a]



s. no.	acid (equiv)	solvent	time (h)	yield (%)[b] 4	5
1	BF_3OEt_2 (0.1)	DCM	24	nd	nd
2	$AlCl_3$ (0.1)	DCM	24	nd	nd
3	conc H_2SO_4 (0.1)	DCM	12	35	nd
4	conc H_2SO_4 (0.1)	H_2O	12	30	nd
5	conc H_2SO_4 (0.1)	THF	12	38	nd
6	conc H_2SO_4 (0.1)	IPA	12	45	5
7	conc H_2SO_4 (0.5)	IPA	12	40	10
8	conc H_2SO_4 (1)	IPA	12	35	10
9	conc H_2SO_4 (5)	IPA	12	25	5
10	CSA (0.1)	DCM	12	45	nd
11	CSA (0.1)	IPA	12	50	25
12	CSA (0.5)	IPA	12	50	15
13	CSA (1)	IPA	12	70	10
14	conc HNO_3 (1)	IPA	12	20	5
15	conc CH_3COOH (1)	IPA	12	20	5
16	TFA (1)	IPA	12	10	trace

[a]Optimized reaction condition: **3** (1 equiv) and camphorsulfonic acid (1 equiv; CSA) in 5 mL of isopropyl alcohol (solvent) at room temperature. TFA = trifluoroacetic acid. IPA = isopropyl alcohol, THF = tetrahydrofuran. [b]Isolated yield, nd = not detected.

room temperature, but the C-8 epoxide decomposed at higher temperatures (multiple spots on TLC), and the reaction was found to be heat sensitive.

The structural identification of intermediate compounds **4** and **5** was unambiguously confirmed by spectroscopy methods (Figure 2) and crystallographic data (single-crystal X-ray diffractometer) (Figure 3). Compound **4** showed a peak at δ 3.63 ppm in ^{1}H NMR spectra for CH_2 proton of the C-17 position with removal of peaks at δ 2.80 and 2.56 ppm associated to C-8 epoxide (**3**). During the comparison of ^{1}H NMR of compounds **4** and **5**, a significant peak at δ 5.69 ppm for a new double bond at C-7,8 position was observed in compound **4**, and no such peak was seen for compound **5**; instead, in ^{1}H NMR of compound **5**, attachment of isopropyl at the C-8 position was observed. In Figure 2, we stacked the ^{1}H NMR of intermediates **4** and **5** to analyze the changes in the ^{1}H NMR pattern of the other positions as well. Notably, the same pattern for the peaks of C-14, C-11, and C-12 has been found with a very slight change in δ value.

Further, DEPT-135 comparison (Figure 4) of compounds **4** and **5** also confirmed the formation of these two intermediate products. The peaks for CH of both **4** and **5** at C-11, C-14, and C-12 remained intact in the aromatic region. The position of C-7 carbon was observed at 122.20 ppm for compound **4** and 30.28 ppm for compound **5** in DEPT-135.

In addition to this, the peaks of CH_2 at C-15, C-19, C-17, C-1, C-2, and C-6 were found to be similar with a very minor change in the chemical shift of **4** and **5** (Figure 4). Further, site-selective reaction at the C-17 position of **4** has been achieved by first protection at C-3 and C-19 hydroxyl groups with benzaldehyde dimethyl acetal (BDA) in dimethyl formamide (DMF) at 60 °C (acetonide protection) resulted C-3, 19 benzal protected 17-hydroxy, 14-deoxy 11,12 didehydroandrographolide (**6**). The OH at the C-17 position has also been confirmed by acylation of **6** with acetic anhydride in pyridine that resulted in compound **7** (Scheme 2).

Compound **6** was used for selective ester formation at the C-17 position. The ester formation at this position was carried out by coupling of 17-OH of compound **6** with different substituted aromatic, aliphatic, and phenyl acetic acids in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in DCM with catalytic 4-dimethylaminopyridine (DMAP) at room temperature that led to different C-17 esters (compounds **8a−y**) of andrographolide with quantitative yields (85−95%) (Scheme 3).

Further, as the parent andrographolide (**1**) contains free hydroxyl at C-3 and C-19 positions, to determine the effect of these hydroxyl groups, we performed C-$_{3,19}$ benzyl deprotection with *p*-toluene sulfonic acid (PTSA) in methanol at room temperature of compounds **8a−y**, resulting in the formation of compounds **9a−y** with a free 3,19-hydroxyl group in good yield (Scheme 4).

The partial correlation of ^{1}H NMR for compound **6**, **8a**, and **9a** is shown in Figure 5, in which compound **6** showed peaks at δ 7.50 to 7.31 ppm for the benzyl group (5H) and one peak at δ 5.77 ppm for H-21. Additional peaks related to the aromatic ester attached at the C-17 position were observed in ^{1}H NMR of product **8a**. Deprotection was also confirmed by the ^{1}H NMR. Disappearance of the aromatic peaks related to the benzyl group (5H) at δ 7.5 to 7.2 ppm and CH-21 singlet at δ 5.7 ppm was observed (Figure 5), and only aromatic peaks associated to the ester group at the C-17 position remained. All of compounds **8a−y** and **9a−y** including parent molecules were screened for anticancer activity.

2.2. Biology. *2.2.1. Cell Growth Inhibition Studies and Structure−Activity Relationship (SAR).* All the synthesized compounds (andrographolide derivatives; **1−7**, **8a−y**, and **9a−y**) were evaluated for anticancer activity against human cancer cell lines A549 (lung carcinoma), PC3 (prostate carcinoma), MCF-7 (breast carcinoma), and HCT-116 (colon carcinoma)

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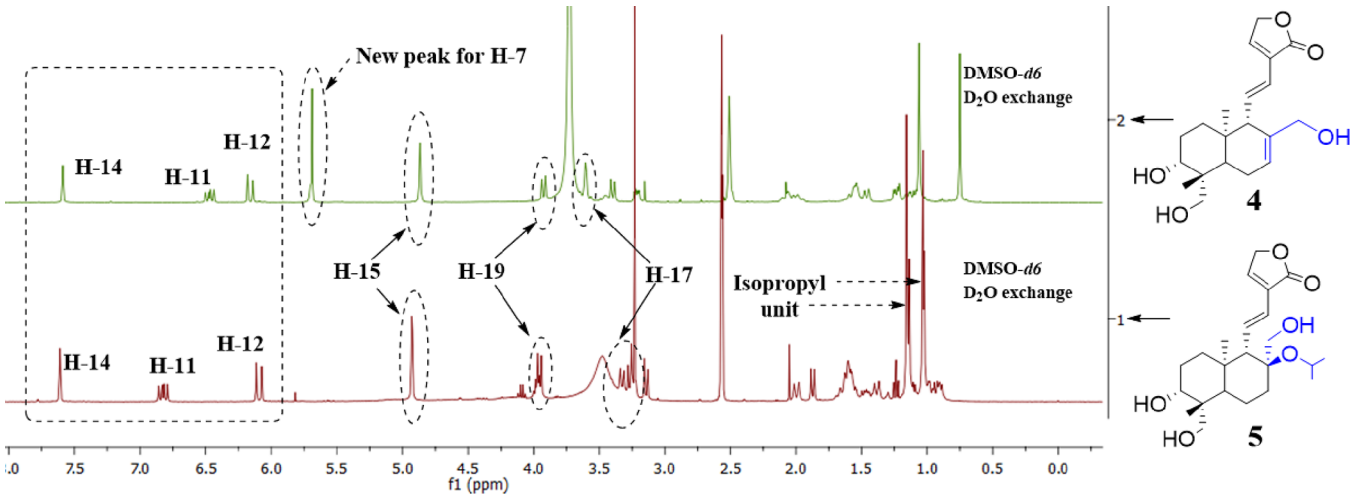

Figure 2. ^{1}H NMR correlation for intermediate compounds **4** and **5.**

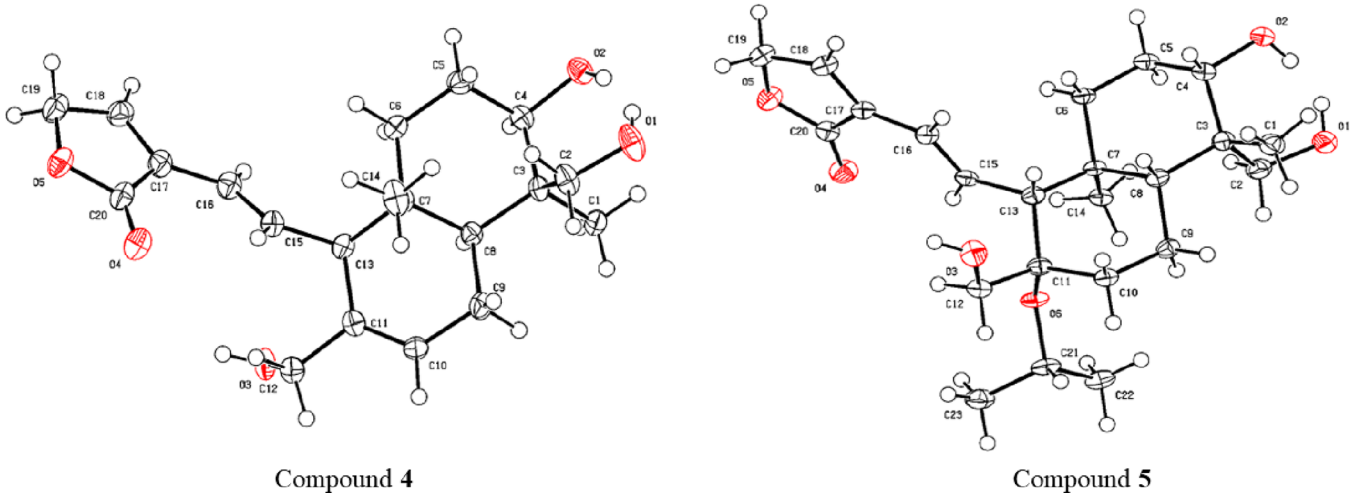

Figure 3. Single-crystal X-ray structures (ORTEP drawing) of intermediate compound **4** (CCDC no. 1941857) and **5** (CCDC no. 2143128) with thermal displacement ellipsoids drawn at the 50% probability.

by using an MTT assay at 20 μM concentration as depicted in Table 2. All synthetic ester derivatives were shown to have higher % age growth inhibition compared to parent compound **1**. Initially, andrographolide (**1**), intermediate compounds (**2**, **3**, **4**, **5**, and **6**), and C-17 acylated (**7**) andrographolide analogues were evaluated and showed good to moderate inhibition activity at 20 μM against the A549 cell line. In the series, we found that compound **7** showed 48% age growth inhibition that encouraged us to synthesize and screen more C-17 aromatic ester derivatives (**8a**−**8n**) of andrographolide, and results showed that most of the compounds were more effective against the A549 cell line than other cell lines (MCF-7, PC-3, and HCT-116). This might be due to differences in sensitivity across the four cell lines. Compound **8a** displayed 72.82% age growth inhibition against the lung cancer (A549) cell line. Thereafter, the C-17 phenyl acetyl ester derivatives of andrographolide were also screened for % age growth inhibition, and it was found that compounds **8s** (78%) and **8u** (72%) showed good inhibition against all the cell lines. The aliphatic ester derivatives (**8w**, **8x**, and **8y**) were also screened against the four cell lines, and better inhibition was found against the A549 cell line than PC-3, MCF-7, and HCT-116 cell lines.

According to reports in the literature, the free hydroxyl group plays an important role in the binding with the targeted receptors. Therefore, C-3,19 deprotected andrographolide derivatives (**9a**−**y**) were also synthesized and evaluated against all the four cell lines and demonstrated less growth inhibition compared to C-3,19 protected andrographolide derivatives (**8a**−**y**), but in some cases, activity increased (**9j**, **9l**, **9m**, **9n**, **9s**, and **9v**).

The structure−activity relationship (SAR) study of synthetic derivatives of andrographolide for the A549 cell line was performed. From SAR studies of compounds **8a**−**n**, we found that **8a** having no substitution on the aromatic ester ring showed 72% growth inhibition against the A549 cell line, more than the parent compound (21% growth inhibition). Meanwhile, further halogen ring substitutions (**8c**−**f**) on the aromatic ester ring did not have a greater impact on the growth inhibition (<50% growth inhibition). Additionally, compounds **8b** and **8j** substituted with mono- and dimethoxy did not provide a potential growth inhibition (<52%). Interestingly, *m*-chloro-*p*-methoxy (**8l**) and *o*-fluoro-*p*-bromo (**8m**) substituted compounds showed improved active growth inhibition than the parent andrographolide (<60% growth inhibition). A significant increase in % cytotoxicity was seen in

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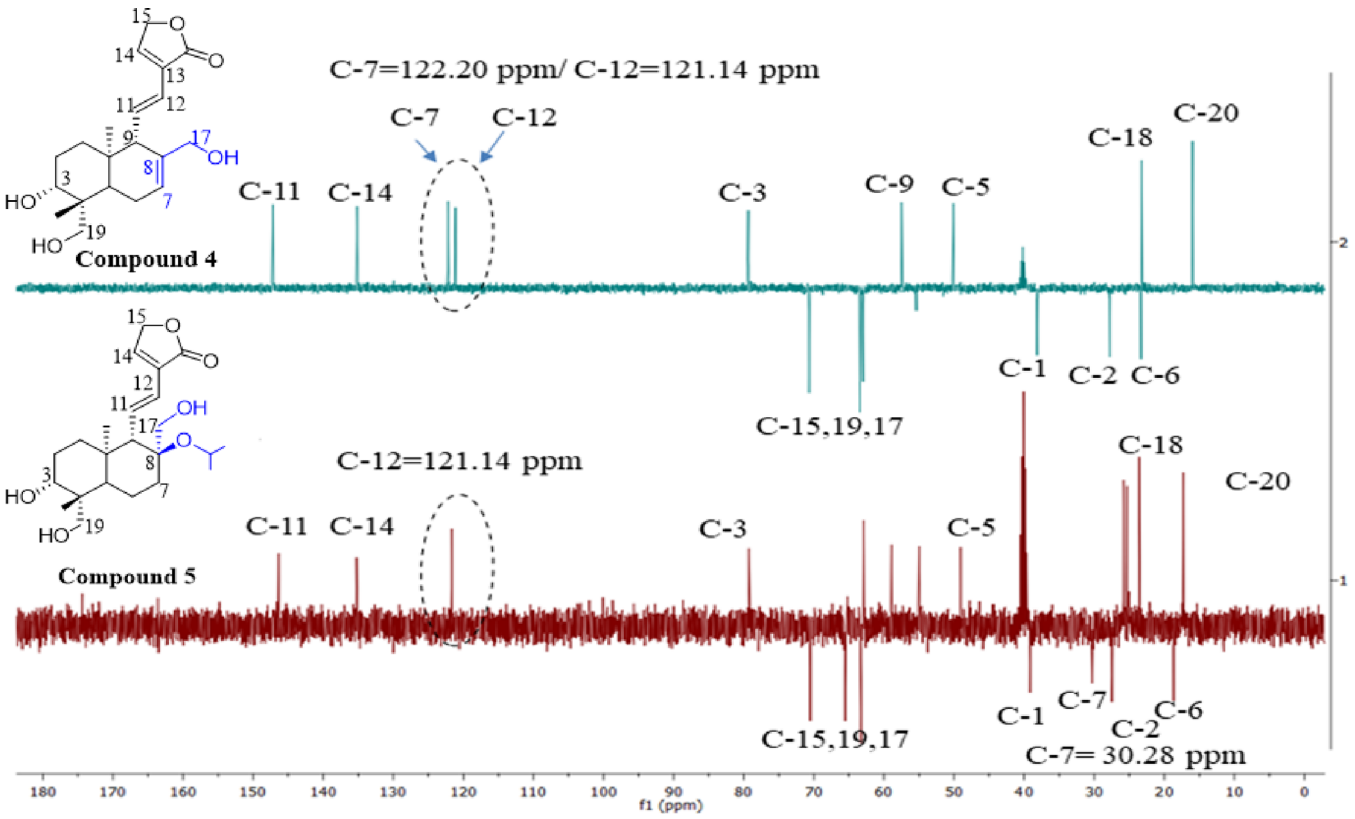
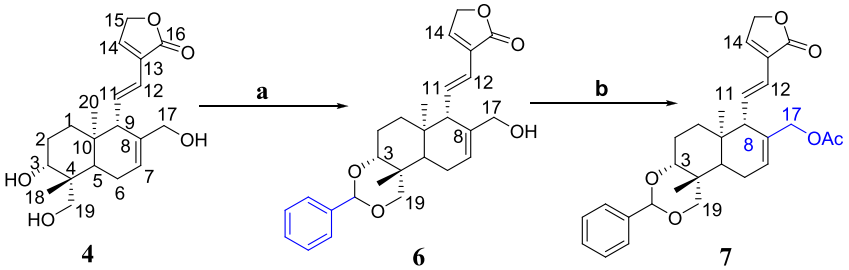


Figure 4. DEPT-135 of intermediate compounds **4** and **5**.

Scheme 2. Compounds 4, 6, and 7[a]



[a]Reagents and conditions: (a) BDA, DMF, 60 °C, 2 h, 90%; (b) Ac_2O, pyridine, rt, 8 h, 61%.

the compound containing *m*-CF_3 (**8h**; 69%) and *m*-CH_3(**8i**; 68%). Later, on the basis of structure−activity relationship analyses of compounds **8o−v**, we discovered that most of the compounds had comparable activity to andrographolide (**1**) against the A549 cell line, with the exception of compound **8s** (78% inhibition), which has *p*-OCH_3, and compound **8u** (72% inhibition), which has *o*,-*m*,-*p*-OCH_3. More interestingly, we observed that aliphatic esters (**8w**, **8x**, and **8y**) showed a good cytotoxic potential against all screened cell lines, indicating that the introduction of the aliphatic chain played an important role in the activity. The SAR studies of compounds **9a−y** with free C-3 and C-19 OH revealed that most of the compounds showed a decrease in % age growth inhibition except compound **9s** (*p*-OCH_3, 82%) and **9v**(*m*-*p*-dichloro; 72%). This predicts that the benzyl group at the C-3,19 position played a significant role in the anticancer activities of these compounds. Among the synthesized derivatives, compound **9s** with a para methoxy substitution exhibited the highest level of cytotoxicity (82% against the A549 cell line) (Figure 6 and Table 2).

2.2.2. Maximal Inhibitory Concentration (IC_{50} Values) Studies. Thereafter, those compounds that showed >70% cell growth inhibition were evaluated for their maximal inhibitory concentration (IC_{50} values). Notably, we found that six compounds—**8a** (10.6 μM), **8s** (6.6 μM), **8u** (5.4 μM), **8w** (8.4 μM), **9s** (3.5 μM), and **9v** (7.5 μM)—against A549 cells and nine compounds—**8p** (8.0 μM), **8r** (5.8 μM), **8s** (5.9 μM), **8u** (9 μM), **8v** (8.4 μM), **9j** (6.1 μM), **9l** (5.7 μM), **9m** (7.6 μM), and **9n** (5.7 μM)—against PC3 cells showed maximal inhibition at IC_{50} less than 10 μM. As shown in Table 3, compounds **8u** and **9s** exhibited more potent cytotoxicity (IC_{50} = 5.4 and 3.5 μM) than andrographolide (IC_{50}: >20 μM) against A549, about 4 and 7 times more potent than andrographolide, respectively. Although the C-17 ester andrographolide derivatives with protection at C-3 and C-19-hydroxyl groups **8a−y** exhibited almost similar cytotoxicity against MCF-7 and HCT-116 cell lines as andrographolide

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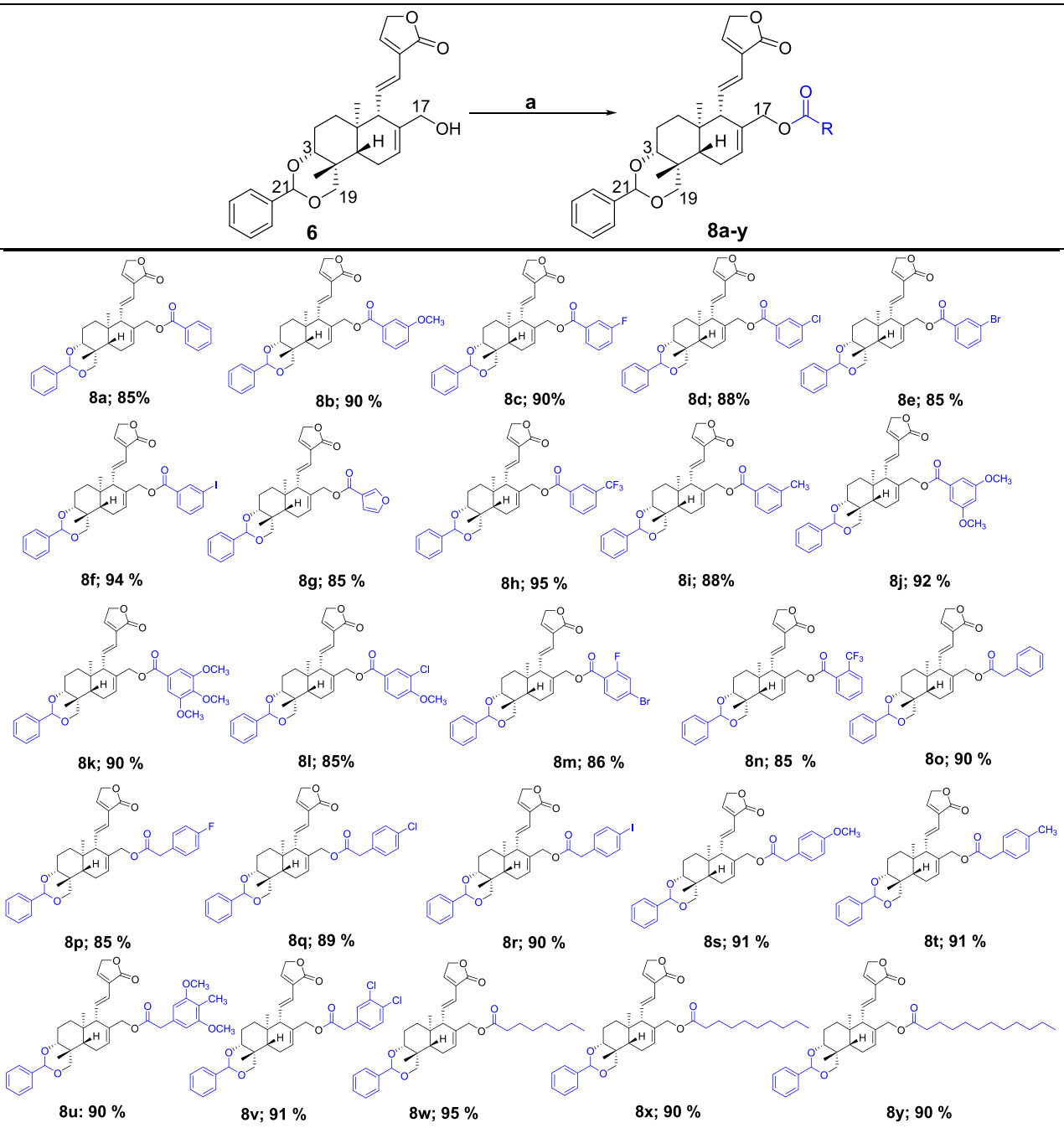
Scheme 3. Synthesis of C-$_{3,19}$ Benzal, C-17 Ester, 14-Deoxy-11,12-didehydroandrographolide (Compounds 8a−y)[a]



[a]Reagents and conditions: (a) R-COOH, EDC, DMAP, DCM, 2 h, room temperature, 85−95%.

(**1**), the same result was observed with free C-3 and C-19 hydroxyl compounds **9a−y** against MCF-7 and HCT-116 cell lines. The compound **9s** was found to be the most potent among the synthesized compounds and selectively showed the maximum inhibition at 3.5 μM concentrations against A549 cells. Furthermore, the most active compound **9s** was considered for further biological investigation on A549 cells.

2.2.3. Expanded Panel of Lung Cancer Cell Lines with Respect to Selectivity Index with Normal Cell Line. Additionally, the *in vitro* cytotoxicity of active compound **9s** was assessed against two additional lung cancer subtypes, HOP92 and HOP62, and its IC_{50} was found to be 38.6 and 13.0 μM, respectively (Table 4). This clearly indicates that the compound is more effective toward A549 cells. Furthermore, compound **9s** was tested against normal human embryonic kidney cells (HEK293); selectivity index (SI), to know its cytotoxic selectivity that is drug safety against cancer cells versus normal cells against these cancer cell lines. A favorable SI >2 indicates a drug with efficacy and high selectivity. Here, the selected compound **9s** was found to exhibit an SI of 13.9, making it a favorable as well as effective drug (Figure 7).

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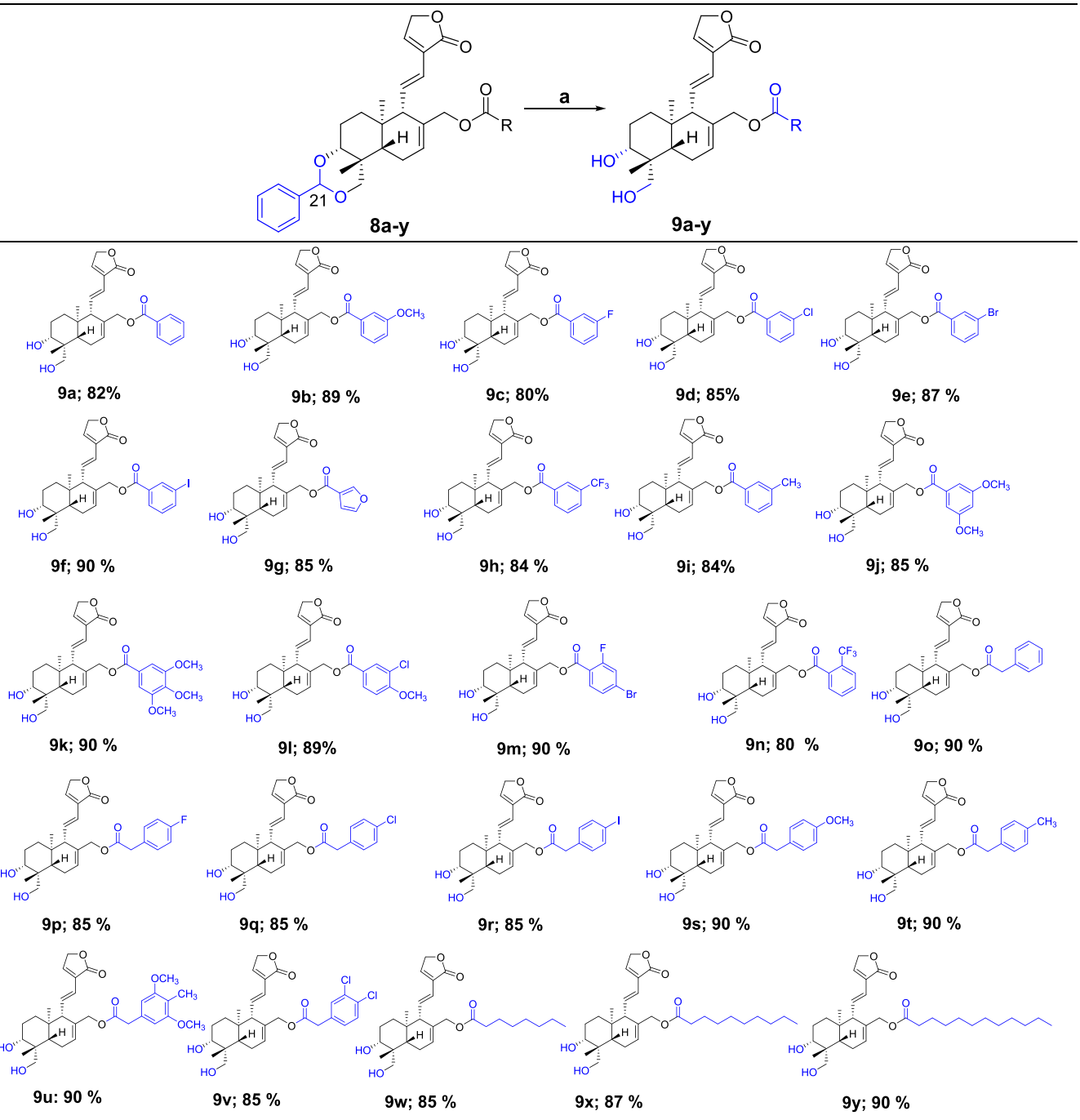
Scheme 4. Synthesis of 3,19-Dihydroxy, C-17 Aryl Ester, 14-Deoxy-11,12-didehydroandrographolide (Compounds 9a−y)[a]



[a](a) Reagents and conditions: *p*-toluene sulfonic acid (PTSA), CH_3OH, 2 h, 80−90%.

*2.2.4. Compound **9s** Induced Nuclear Morphology in A549 Cells.* To determine the role of **9s** in cell growth inhibition, morphological alterations in A549 cells were assessed by fluorescence microscopy (Figure 8). The 4′,6-diamidino-2-phenylindole (DAPI) staining indicates nuclear alterations/shrinkage, chromatin condensation, apoptotic bodies, and membrane blebbing, which are features of apoptosis. The A549 cells were treated with 1, 3.5, and 5 μM concentrations of **9s** for 48 h. Cisplatin was used as a positive control for the experiment.

In the untreated A549 cells, the stained nuclei in the cells appeared rounded as well as homogeneously stained, whereas treated A549 cells showed an altered staining pattern, apoptotic bodies, and condensed chromatin, which are hallmarks of apoptosis.

*2.2.5. Compound **9s** Induced Intracellular ROS Production in A549 Cells.* Reactive oxygen species (ROS) are defined as highly reactive, unstable molecules that are created as a part of normal metabolic processes. As their increased levels disrupt cellular proteins, lipids, and nucleic acids, which can eventually cause cells to undergo apoptosis, their rise may be an

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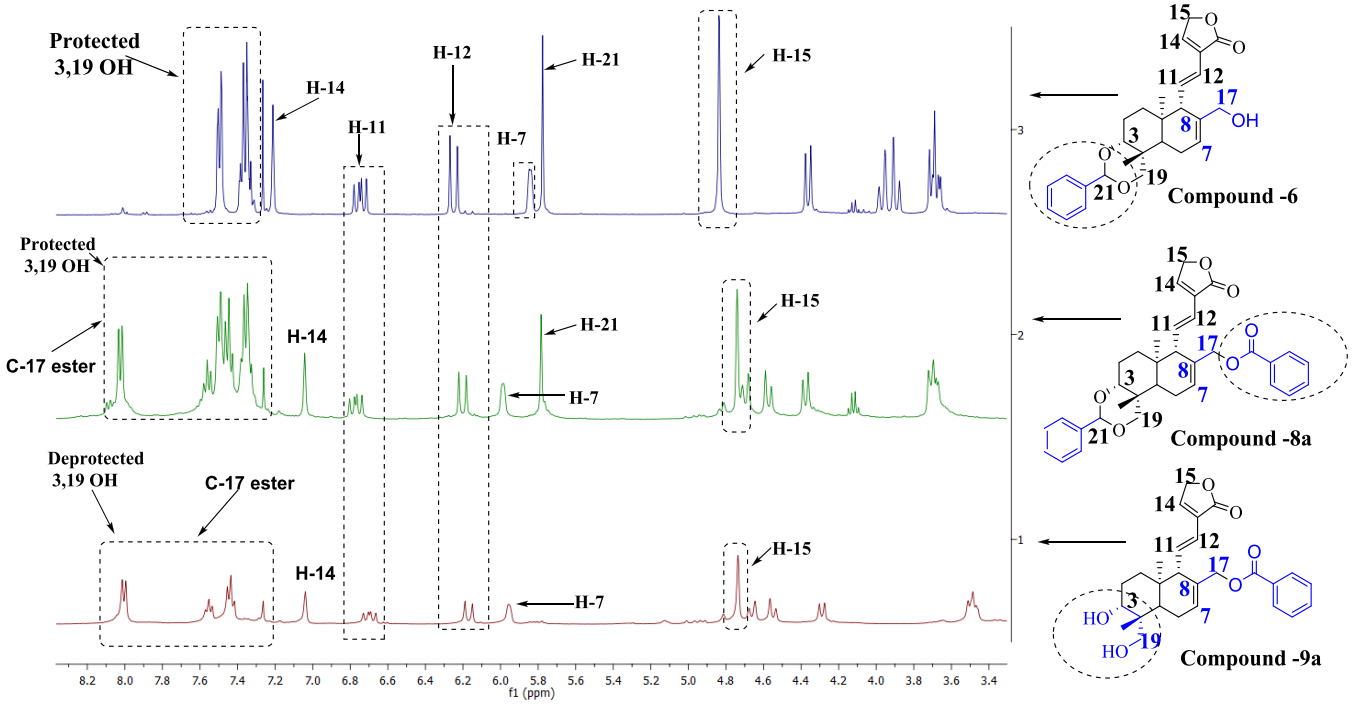

Figure 5. The partial ^{1}H NMR correlation for compounds **6**, **8a**, and **9a**.

indication that cancer cells are undergoing this process. In this study, A549 cells were seeded after respective treatment with different concentrations of compound **9s**, i.e., 1, 3.5, and 5 μM, for 48 h. The cells were stained with DCFDA dye to assess the intracellular ROS levels by fluorescence microscopy. H_2O_2 was used as a positive control, as it induces ROS. We observed that the molecule **9s** significantly induced more ROS generation in A549 cells at 1 μM concentration (Figure 9). ROS can dynamically influence the microenvironment of tumors, which can initiate angiogenesis and metastasis at different concentrations. At low to moderate concentrations, ROS can also activate the cancer cell survival signaling cascades that involve MAPK/ERK1/2 and PI3K/Akt pathways.

Therefore, this can critically depend upon the ROS levels that can target the dual action of ROS with respect to concentration bias. In this experiment, we have observed that at 3.5 and 5 μM concentrations, ROS levels decrease, but at 1 μM, ROS generation was increased comparable with the H_2O_2.

*2.2.6. Compound **9s** Induced Mitochondrial Membrane Potential (MMP) Loss in A549 Cells.* Rhodamine-123 (Rh-123) dye was used to detect alterations in mitochondrial potential (Figure 10). The loss of MMP generates Rh-123 leakage, which lowers fluorescence intensity and ultimately results in cell death, when the permeability of the mitochondria is disrupted. The loss of integrity in the mitochondrial membrane is correlated with a fluorescence degradation. A549 cells were seeded after respective treatment with different concentrations of compound **9s**, i.e., 1, 3.5, and 5 μM, for 48 h. The cells were stained with Rh-123 dye to observe its fluorescence intensity. We have found a significant reduction in MMP after treatment with compound **9s** in comparison with untreated cells.

3. CONCLUSIONS

In summary, a series of C-17 ester derivatives of andrographolide were successfully synthesized and characterized. The biological results indicate that most of the compounds showed activity against lung cancer (A549 cell line) and prostate carcinoma (PC-3 cell line). Among the synthesized compounds, **8s** inhibited cell proliferation effectively in A549 and PC-3 cell variants, and compound **9s** selectively induced apoptosis at IC_{50} = 3.5 μM concentration in the A549 cell line. As per the *in vitro* screening of **9s** against a panel of human lung carcinomas, i.e., HOP92 and HOP62, the study revealed an IC_{50} value of 38.6 and 13 μM, and as per screening of **9s** against normal human embryonic kidney cells (HEK293), a favorable selectivity index (SI) of 13.9 was found. The mechanistic study revealed that compound **9s** induces apoptosis, increases reactive oxygen species (ROS), and disturbs mitochondrial membrane potential. A 7-fold enhancement in the activity against the lung cancer (A549 cell line) of compound **9s** compared to parent andrographolide (**1**) makes it a promising structural lead for the development of new anticancer drugs.

4. EXPERIMENTAL SECTION

4.1. Chemistry. *4.1.1. General Information.* The reaction progress and purity of the andrographolide (**1**) and its derivatives were checked by thin-layer chromatography using Merck precoated silica gel 60 F254 plates. TLC visualization was attained under UV light at 254 nm or exposure to iodine vapors. A Buchi Rotavapor was used for concentration of organic solvents. Column chromatography using silica gels (60−120, 100−200 mesh) was performed for purification of synthesized compounds. NMR spectra (^{1}H and ^{13}C) were recorded on Bruker DPX 400 and DPX 500 using $CDCl_3$, CD3OD, D_2O, and DMSO-d_6 as solvent and TMS as an internal standard. The chemical shifts (δ) are expressed in parts per million (ppm) referenced to the residual solvent, and the coupling constant (J value) is given in hertz (Hz). The MestReNova software was used for processing of NMR spectra, and signal multiplicity is expressed as follows: s

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Table 2. Cytotoxic Activity (% Growth Inhibition) for Ester Derivatives of Andrographolide at 20 μM Concentration

		tissue cell line			
s. no.	compounds	A549 (lung carcinoma)	PC-3 (prostate carcinoma)	MCF-7 (breast carcinoma)	HCT-116 (colon carcinoma)
1	**1**	21.64 ± 0.22	0	42.93 ± 0.05	4.86 ± 0.25
2	**2**	34.31 ± 0.18	0	5.52 ± 0.22	0
3	**3**	20.50 ± 0.20	0	15.18 ± 0.11	0
4	**4**	40.83 ± 0.22	0	4.03 ± 0.13	3.79 ± 0.31
5	**5**	13.2 ± 1.8	55 ± 2.4	17 ± 2.6	59 ± 1.5
6	**6**	32.79 ± 0.01	0	0	34.74 ± 0.32
7	**7**	48.22 ± 0.27	29 ± 0.88	2.87 ± 0.10	39.92 ± 0.11
8	**8a**	72.82 ± 0.05	0	9.68 ± 0.14	21.12 ± 0.19
9	**8b**	48.88 ± 0.17	0	6.04 ± 0.12	11.72 ± 0.11
10	**8c**	41.72 ± 0.45	0	2.06 ± 0.04	19.27 ± 0.37
11	**8d**	30.11 ± 0.11	0	2.40 ± 0.084	0
12	**8e**	31.59 ± 0.23	0	0	0
13	**8f**	30.98 ± 0.25	0	0	33.25 ± 0.11
14	**8g**	40.95 ± 0.39	25 ± 0.58	0	0
15	**8h**	69.48 ± 0.42	54 ± 0.62	0	4.80 ± 0.02
16	**8i**	67.66 ± 0.23	0	4.37 ± 0.01	4.35 ± 0.54
17	**8j**	51 ± 0.48	55.8 ± 0.49	48 ± 0.91	47.2 ± 0.75
18	**8k**	20.4 ± 0.73	5.6 ± 0.59	46 ± 0.77	50 ± 0.62
19	**8l**	61.6 ± 0.83	62 ± 0.97	51 ± 0.50	36.2 ± 0.80
20	**8m**	65 ± 0.50	0	44 ± 0.24	30.4 ± 0.90
21	**8n**	18 ± 1.4	55 ± 0.56	55 ± 0.69	31.3 ± 0.89
22	**8o**	20.13 ± 0.02	0	32.09 ± 0.08	24.97 ± 0.16
23	**8p**	17 ± 1.7	77 ± 0.86	0	20.6 ± 0.95
24	**8q**	11 ± 1.0	39 ± 0.82	46 ± 0.72	36.1 ± 0.96
25	**8r**	2.9 ± 0.69	77 ± 0.48	42 ± 0.69	22.1 ± 0.58
26	**8s**	78 ± 0.97	75 ± 0.93	54 ± 0.53	22.1 ± 0.44
27	**8t**	48.9 ± 0.73	69.5 ± 0.74	27 ± 0.29	45.9 ± 0.86
28	**8u**	72 ± 0.54	70.9 ± 0.41	43 ± 0.28	10.9 ± 0.99
29	**8v**	41.6 ± 0.98	70.3 ± 0.54	34 ± 0.28	12.5 ± 0.78
30	**8w**	70.7 ± 0.73	49 ± 0.85	51 ± 0.96	40.5 ± 0.91
31	**8x**	49.7 ± 0.79	39 ± 0.24	45 ± 0.98	50.1 ± 0.40
32	**8y**	71 ± 0.77	32 ± 0.66	51 ± 0.35	40.1 ± 0.80
33	**9a**	48.99 ± 0.23	49 ± 0.44	14.37 ± 0.01	8.39 ± 0.37
34	**9b**	39.85 ± 0.26	7 ± 0.58	14.60 ± 0.09	0
35	**9c**	42.92 ± 0.27	0	1.54 ± 0.03	14.82 ± 0.17
36	**9d**	49.19 ± 0.20	0	10.02 ± 0.02	30.21 ± 0.15
37	**9e**	50.55 ± 0.17	0	1.93 ± 0.10	14.05 ± 0.24
38	**9f**	58.00 ± 0.15	49 ± 1.0	21.75 ± 0.06	0
39	**9g**	63.58 ± 0.08	11 ± 0.22	0	11.28 ± 0.10
40	**9h**	28.81 ± 0.03	29 ± 1.4	30.4 ± 0.36	3.31 ± 0.13
41	**9i**	21.35 ± 0.42	0	2.09 ± 0.07	0
42	**9j**	8.7 ± 0.45	70 ± 0.82	51 ± 0.49	23.9 ± 0.49
43	**9k**	29.4 ± 0.82	67 ± 0.6.9	41 ± 0.87	19.8 ± 0.68
44	**9l**	3.3 ± 0.63	71.4 ± 0.56	47 ± 0.24	27.5 ± 0.94
45	**9m**	14.9 ± 0.24	78.9 ± 0.96	8 ± 0.85	23.1 ± 0.84
46	**9n**	5.6 ± 0.14	72.2 ± 0.41	18 ± 0.58	44.9 ± 0.78
47	**9o**	43.40 ± 0.19	15 ± 0.72	29.2 ± 0.29	0
48	**9p**	32.6 ± 0.96	44 ± 0.89	12 ± 0.85	27.6 ± 0.31
49	**9q**	47.2 ± 0.85	38 ± 0.96	28 ± 0.87	19.3 ± 0.97
50	**9r**	2.4 ± 0.19	10.6 ± 0.22	12 ± 0.96	27.2 ± 0.48
51	**9s**	82.2 ± 0.78	27.6 ± 0.89	54 ± 0.74	4.1 ± 0.97
52	**9t**	49.7 ± 0.92	52 ± 0.85	5.2 ± 0.5	13.9 ± 0.64
53	**9u**	32.6 ± 0.38	48.7 ± 0.96	69 ± 0.58	35.9 ± 0.87
54	**9v**	72.7 ± 0.54	26.5 ± 0.54	29 ± 0.78	5.7 ± 6.1
55	**9w**	16.8 ± 0.93	67 ± 0.75	25 ± 0.36	23.9 ± 0.58
56	**9x**	23.2 ± 0.74	24 ± 0.83	46 ± 0.84	2.7 ± 0.51
57	**9y**	1.6 ± 0.98	66 ± 0.47	38 ± 0.18	4.6 ± 0.44

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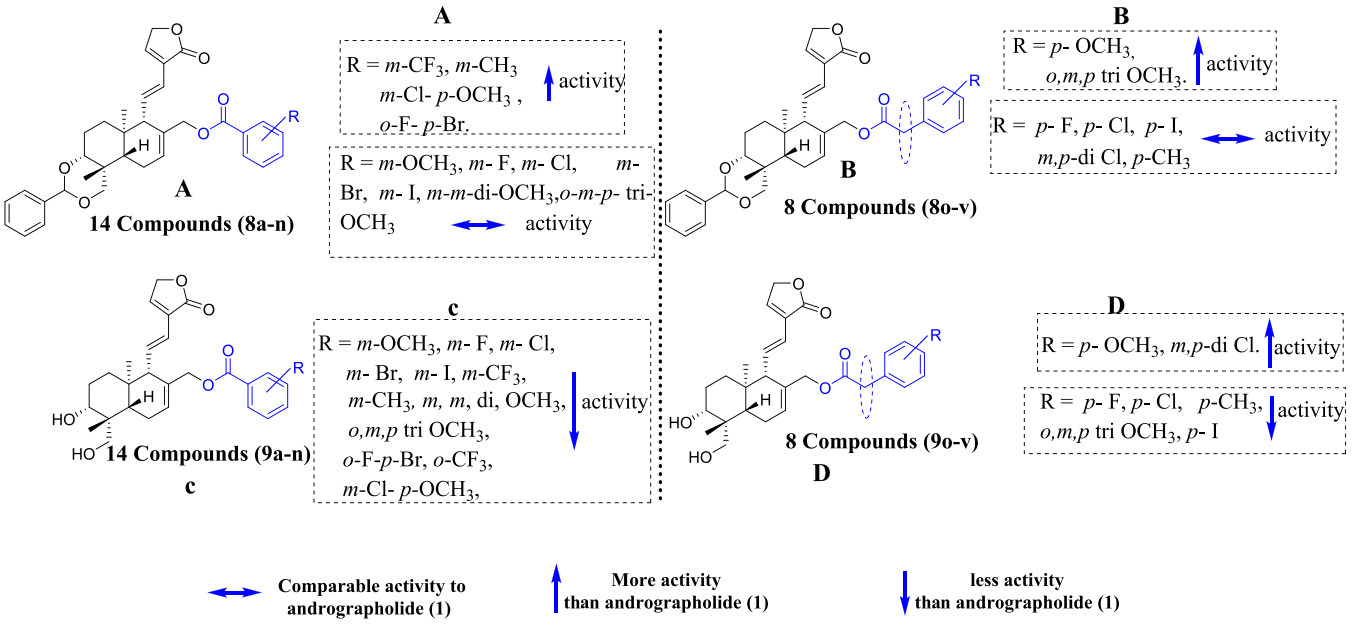

Figure 6. Structure−activity relationship of C-17 ester derivatives of andrographolide in the A549 cell line.

Table 3. Results of Screening Using the MTT Assay[a]

s. no.	compd.	IC_{50} (μM) A549 (lung carcinoma)	PC-3 (prostate carcinoma)	MCF-7 (breast carcinoma)	HCT-116 (colon carcinoma)
1	**1**	>20	>20	>20	>20
2	**8a**	10.6	>20	>20	>20
3	**8p**	>20	8.0	>20	>20
4	**8r**	>20	5.8	>20	>20
5	**8s**	**6.6**	**5.9**	16.9	>20
6	**8u**	5.4	9.0	>20	>20
7	**8v**	>20	8.4	>20	>20
8	**8w**	8.4	>20	20.0	>20
9	**8y**	11.0	>20	20.0	>20
10	**9j**	>20	6.1	16.6	>20
11	**9l**	>20	5.7	17.8	>20
12	**9m**	>20	7.6	>20	>20
13	**9n**	>20	5.7	>20	>20
14	**9s**	**3.5**	>20	14.6	>20
15	**9v**	7.5	>20	>20	>20

[a]Three biological repetitions serve as the basis for calculating **IC_{50} values. The concentrations causing 50% growth inhibition of the cell populations (IC_{50}) were determined from concentration-dependent curves using the GraphPad Prism 7.0 Software. Differences were considered statistically significant for Student *t* criterion <0.05.

Table 4. Expanded Panel of Lung Cancer Cell Lines with Respect to Selectivity Index with the Normal Cell Line

s. no.	cell line (lung carcinoma)	IC_{50} (**9s**)	selectivity index (SI) wrt HEK cell line
1	A549	3.5 μM	13.9
2	HOP92	38.6 μM	1.26
3	HOP62	13 μM	3.7

(singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). HRMS (high-resolution mass spectra) were taken from an Agilent Technology instrument (6540). Unless indicated, all the reagents and solvents used for synthesis and purification were purchased from Sigma-Aldrich/Merck and used as such without further purification.

4.1.2. Andrographolide (1). Andrographolide has been isolated as previously reported in the literature.[42] ^{1}H NMR (400 MHz, CD_3OD) δ 6.84 (H-12, td, J = 6.8, 1.5 Hz, 1H), 5.00 (H-14, d, J = 5.9 Hz, 1H), 4.88 (H-17b, s, 1H), 4.66(H-17a, s, 1H), 4.45 (H-15b, dd, J = 10.2, 6.1 Hz, 1H), 4.15 (H-15a, dd, J = 10.2, 2.0 Hz, 1H), 4.11 (H-19b, d, J = 11.0 Hz, 1H), 3.38 (H-19a, H-3, m, 2H), 2.65−2.54 (H-11, m, 2H), 2.45−2.38 (H-7b, m, 1H), 2.07−1.98 (H-7a, m, 1H), 1.91 (H-9, m, 1H), 1.84−1.76 (H-2, H-1b, H-6b, m, 4H), 1.39−1.28 (H-5, H-6a, H-1a, m, 3H), 1.21 (H-18, s, 3H), 0.74 (H-20, s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.26 (C-16), 147.92 (C-12), 147.39 (H-8), 128.42 (C-13), 107.84 (C-17), 79.54 (C-3), 74.73 (C-15), 65.27 (C-14), 63.62 (C-19), 56.01 (C-9), 54.98 (C-5), 42.32 (C-4), 38.60 (C-10), 37.61 (C-7), 36.78 (C-1), 27.66 (C-2, C-7), 24.35 (C-11), 23.83 (C-6), 22.03 (C-18), 14.20 (C-20). HRMS (ESI) m/z calcd for $C_{20}H_{31}O_5$ $[M + H]^+$ 351.2171, found 351.2152.

4.1.3. Preparation of 14-Deoxy-11,12-didehydroandrographolide (2). Al_2O_3 (15.2 g, 0.15 moL) was added to the solution of **1** (10.0 g, 0.03 moL) in dry pyridine (20.00 mL). The mixture was refluxed at 115 °C for 12 h and then filtrated to remove the Al_2O_3. The filter cake was washed with EtOAc. The filtrate was evaporated under a vacuum to give a crude mixture containing 14-deoxy-11,12-didehydroandrographolide (**2**). The crude mixture was washed with sat. $CuSO_4{\cdot}5H_2O$ (3 × 350 mL), H_2O (350 mL), and brine (300 mL); dried over anhydrous Na_2SO_4; and then concentrated under reduced pressure. The residues were purified by silica gel column chromatography (3% methanol/dichloromethane) to give pure compound **2** in 76% yield (7.0 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (H-14, s, 1H), 6.87 (H-11, dd, J = 15.8, 10.1 Hz, 1H), 6.12 (H-12, d, J = 15.8 Hz, 1H), 4.84 (H-15, d, J = 13.5 Hz, 2H), 4.78 (H-17b, d, J = 1.4 Hz, 1H), 4.52 (H-17a, d, J = 1.3 Hz, 1H), 4.22 (H-19b, d, J = 11.0 Hz, 1H), 3.47 (H-3, dd, J = 11.4, 4.4 Hz, 1H), 3.34 (H-19a, d, J = 11.0 Hz, 1H), 2.45 (H-7b, ddd, J = 13.5, 3.8, 2.1 Hz, 1H), 2.32 (H-9, d, J = 10.0 Hz, 1H), 2.04 (H-7a, td, J = 13.4, 4.7 Hz, 1H),

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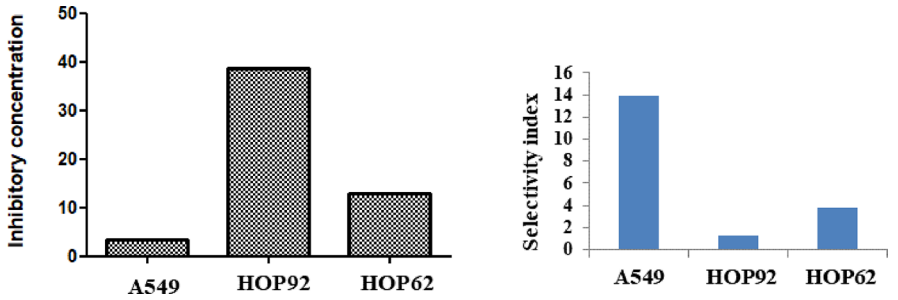

Figure 7. Bar graph displaying the selectivity index and IC_{50} of compound **9s** for a panel of human lung carcinomas. The data reflect the mean and standard deviation of three separate experiments. Significance is indicated by an asterisk, ***$p < 0.001$.

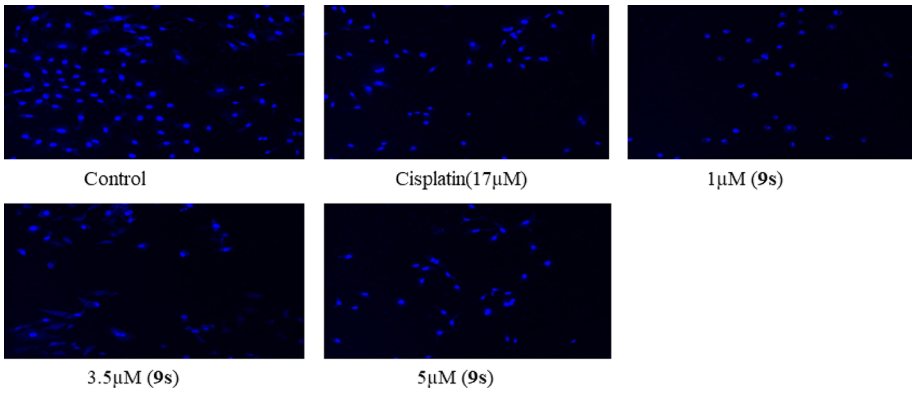

Figure 8. Effect of compound **9s** at various doses on the A549 cell line's nuclear morphology when stained with DAPI. Cisplatin (17 μM) was used as a positive control.

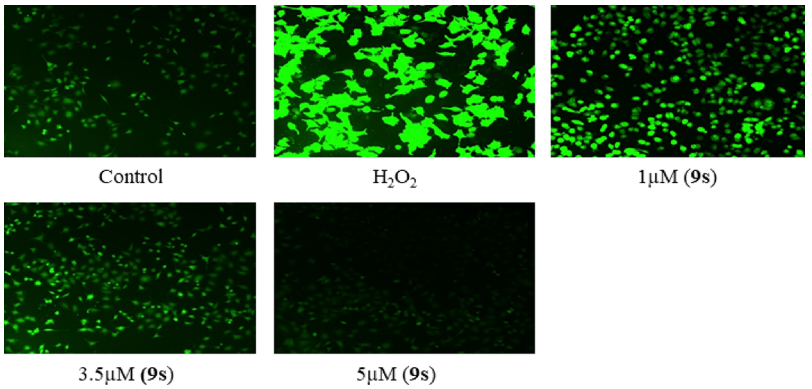

Figure 9. Effect of compound **9s** with different concentrations over ROS generation in the A549 cell line using DCFDA dye. Cisplatin was taken as positive control (17 μM).

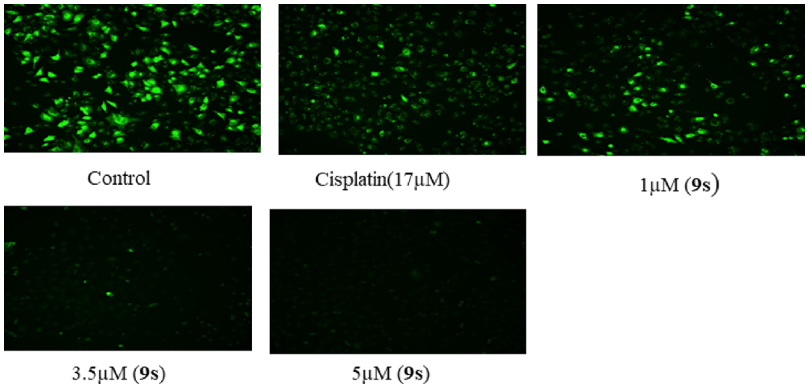

Figure 10. Mitochondrial membrane potential was measured using Rh-123 dye on treatment with different concentrations of **9s** in A549 cells. Cisplatin was used as positive control (17 μM).

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1.85−1.68 (H-2, H-1b, m, 3H), 1.51 (H-1a, dt, J = 13.5, 3.3 Hz, 1H), 1.35 (H-5, dd, J = 12.9, 4.2 Hz, 1H), 1.26 (H-18, s, 3H), 1.22−1.10 (H-6, m, 2H), 0.81 (H-20, s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.42 (C-16), 148.13 (C-8), 143.07 (C-14), 136.00 (C-11), 129.24 (C-13), 121.09 (C-12), 109.17 (C-17), 80.77 (C-3), 69.70 (C-15), 64.20 (C-19), 61.66 (C-9), 54.66 (C-5), 42.91 (C-4), 38.57 (C-10), 38.25 (C-7), 36.57 (C-1), 28.07 (C-2), 22.97 (C-18), 22.68 (C-6), 15.92 (C-20). HRMS (ESI) m/z calcd for $C_{20}H_{27}O_4$ $[M + H]^+$ 331.1909, found 331.1900.

*4.1.4. Synthesis of 8,17-Epoxy-14-deoxy-11,12-didehydroandrographolide (**3**).* To a stirred solution of **2** (2.0 g, 6.0 mmoL) in CH_2Cl_2 was added *meta*-chloroperoxybenzoic (1.55 g, 9.0 mmoL) at room temperature. After stirring was continued for 2.0 h, the reaction mixture was diluted with EtOAc and quenched with sat. $NaHCO_3$. The mixture was extracted with dichloromethane (100 mL × 3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (5% methanol/dichloromethane) to give (**3**) in 92% yield (1.92 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (H-14, t, J = 1.9 Hz, 1H), 6.53 (H-11, dd, J = 15.5, 9.8 Hz, 1H), 6.16 (H-12, d, J = 15.6 Hz, 1H), 4.79 (H-15, d, J = 1.6 Hz, 2H), 4.23 (H-19a, d, J = 11.0 Hz, 1H), 3.48 (H-3, dd, J = 11.3, 4.3 Hz, 1H), 3.37 (H-19b, d, J = 11.1 Hz, 1H), 2.83−2.78 (H-17a, m, 1H), 2.57 (H-17b, d, J = 4.4 Hz, 1H), 2.16 (H-9, d, J = 9.8 Hz, 1H), 1.96−1.79 (H-7, H-2a, H-1, m, 5H), 1.50 (H-6, H-5, H-2b, m, 4H), 1.28 (H-18, s, 3H), 0.97 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.05 (C-16), 143.90 (C-11), 130.83 (C-14), 128.56 (C-13), 123.88 (C-12), 80.42 (C-3), 69.46 (C-15), 63.89 (C-19), 58.98 (C-9), 58.01 (C-8), 54.10 (C-5), 50.79 (C-17), 42.67 (C-4), 38.71 (C-10), 37.81 (C-1), 35.34 (C-7), 27.41 (C-2), 22.61 (C-6), 21.08 (C-18), 15.88 (C-20). HRMS (ESI) m/z calcd for $C_{20}H_{27}O_5$ $[M + H]^+$ 347.1858, found 347.1843.

*4.1.5. Synthesis of Compounds 3,19,17-Trihydoxy-14-deoxy-11,12-didehydroandrographolide (**4**) and 3,19,17-Trihydoxy,8-isopropyl-14-deoxy-11,12-didehydroandrographolide (**5**).* Optimized reaction condition: To a stirred solution of **3** (500 mg, 1.43 mmoL, 1 equiv) in isopropyl alcohol (IPA) (5 mL) was added camphorsulfonic acid (CSA) (334.51 mg, 1.43 mmoL, 1 equiv) at room temperature. After stirring was continued for 6 h, the reaction mixture was diluted with EtOAc and quenched with sat. $NaHCO_3$. The mixture was extracted with EtOAc (×3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (3% methanol/dichloromethane) to give **4** in 70% yield (350 mg) and **5** in 10% yield (59 mg) as white solids. This reaction was repeated many times for the preparation of compound **4** for C-17 ester derivatives. Compound **4**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (H-14, s, 1H), 6.47 (H-11, dd, J = 15.7, 10.5 Hz, 1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.69 (H-7, s, 1H), 4.87 (H-15, s, 2H), 3.92 (H-19a, d, J = 11.0 Hz, 1H), 3.60 (H-17, br, 2H), 3.40 (H-19b, d, J = 10.9 Hz, 1H), 3.21 (H-3, dd, J = 10.5, 4.8 Hz, 1H), 2.18−1.83 (H-9, H-6, m, 3H), 1.61−1.43 (H-5, H-2, m, 3H), 1.23 (H-1, m, 2H), 1.06 (H-18, s, 3H), 0.75 (H-20, s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.86 (C-16), 147.01 (C-11), 137.01 (C-8), 135.24 (C-14), 127.53 (C-13), 122.18 (C-7), 121.23 (C-12), 79.40 (C-3), 70.63 (C-15), 63.47 (C-19), 62.99 (C-17), 57.53 (C-9), 50.13 (C-5), 42.13 (C-4), 38.79 (C-10), 38.59 (C-1), 27.81 (C-2), 23.34 (C-6), 23.25 (C-18), 15.97 (C-20). HRMS (ESI) m/z calcd for $C_{20}H_{28}O_5Na$ $[M + Na]^+$ 371.1834, found 371.1844. Compound **5**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (H-14, s, 1H), 6.83 (H-11, dd, J = 16.2, 10.1 Hz, 1H), 6.09 (H-12, d, J = 16.2 Hz, 1H), 4.93 (H-15, s, 2H), 3.96 (H-19a, d, J = 5.0 Hz, 1H), 3.35−3.26 (H17, H-19b, H-21; CH-isopropyl, m, 4H), 3.14 (H-3, d, J = 10.2 Hz, 1H), 2.00 (H-9, d, J = 14.2 Hz, 1H), 1.81−1.26 (H-7, H-6, H-5, H-2, H-1, H-21, m, 9H), 1.15 (H-22; isopropyl unit, br, 3H), 1.14 (H-18, s, 3H), 1.03 (H-23; isopropyl unit , d, J = 1.7 Hz, 3H), 1.02 (H-20, s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.82 (C-16), 146.28 (C-11), 135.25 (C-14), 127.92 (C-13), 121.65 (C-12), 79.27 (C-3), 78.93 (C-8), 70.50 (C-15), 65.55 (C-21), 63.30 (C-19), 62.87 (C-17), 58.96 (C-9), 49.05 (C-5), 42.79 (C-4), 37.22 C-10), 30.32 (C-7), 27.52 (C-2), 25.82 (C-22), 25.33 (C-23), 23.58 (C-6), 18.66 (C-18), 17.28 (C-20). HRMS (ESI) m/z calcd for $C_{23}H_{36}O_6Na$ $[M + Na]^+$ 431.2410, found 431.2408.

*4.1.6. 3,19-Benzal-17-hydroxy-14-deoxy-11,12-didehydroandrographolide (**6**).* To a stirred solution of **4** (1.44 mmoL, 500 mg) in DMF (10 mL) was added camphorsulfonic acid (CSA) (0.144 mmoL, 33.45 mg) and benzaldehyde dimethyl acetal (BDA) (2.88 mmoL, 438.30 mg) at 60 °C. After stirring was continued for 2 h, the reaction mixture was diluted with EtOAc and quenched with sat. $NaHCO_3$. The mixture was extracted with EtOAc (200 mL × 3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (40% EtOAc: Hexane) to give **6** in 90% yield (564 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (Ar-H, m, 2H), 7.39−7.33 (Ar-H, m, 3H), 7.21 (H-14, s, 1H), 6.75 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.25 (H-12, d, J = 15.7 Hz, 1H), 5.85 (H-7, s, 1H), 5.78 (H-21, s, 1H), 4.84 (H-15, s, 2H), 4.36 (H-17a, d, J = 11.4 Hz, 1H), 3.97 (H-17b, d, J = 12.9 Hz, 1H), 3.89 (H-19a, d, J = 13.0 Hz, 1H), 3.73−3.64 (H-19b, H-3, m, 2H), 2.65 (H-9, d, J = 10.5 Hz, 1H), 2.46−2.25 (H-6, m, 2H), 1.91 (H-2, d, J = 13.0 Hz, 2H), 1.84−1.76 (H-1, m, 2H), 1.72 (H-5, dd, J = 9.0, 4.1 Hz, 1H), 1.49 (H-18, s, 3H), 1.02 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.38 (C-16), 143.72 (C-11), 138.87 (C-Ar), 136.86 (C-8), 136.02 (C-14), 128.91 (C-13), 128.37 (C-Ar), 126.22 (C-Ar), 124.08 (C-7), 122.34 (C-12), 95.29 (C-21), 81.47 (C-3), 69.75 (C-15), 69.57 (C-19), 65.61 (C-17), 57.46 (C-9), 49.46 (C-5), 37.19 (C-4), 36.32 (C-10), 36.05 (C-1), 25.68 (C-2), 22.22 (C-6), 21.23 (C-18), 15.92 (C-20). HRMS (ESI) m/z calcd for $C_{27}H_{32}O_5Na$ $[M + Na]^+$ 459.2147, found 459.2154.

*4.1.7. 3,19-Benzal-17-OAc-14-deoxy-11,12-didehydroandrographolide (**7**).* To a stirred solution of **6** (100 mg, 0.23 mmoL) in pyridine (Py) (5 mL) was added acetic anhydride (Ac_2O, 23.48 mg, 0.23 mmoL) at 115 °C. After stirring was continued for 6 h, the reaction mixture was diluted with EtOAc and quenched with sat. $NaHCO_3$. The mixture was extracted with EtOAc (×3). The combined organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/hexane) to give **7** in 61% yield (67 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.49 (Ar-H, m, 2H), 7.41−7.34 (Ar-H, m, 4H), 7.21 (H-14, s, 1H), 6.74 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.22 (H-12, d, J = 15.7 Hz, 1H), 5.91 (H-7, s, 1H), 5.79 (H-21, s, 1H), 4.84 (H-15, s, 2H), 4.41−4.33 (H-17, m, 2H), 4.14 (H-19a, q, J = 7.1 Hz, 1H), 3.75−3.67 (H-19b, H-3, m,

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2H), 2.64 (H-9, d, J = 10.1 Hz, 1H), 2.50−2.34 (H-6, m, 2H), 2.05 (H-OAc s, 3H), 1.98−1.88 (H-2, m, 2H), 1.86−1.79 (H-1, m, 2H), 1.75 (H-5, dd, J = 9.3, 4.0 Hz, 1H), 1.51 (H-18, s, 3H), 1.05 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.11 (C-16), 170.81 (C-28), 143.57 (C-11), 138.87 (C-Ar), 135.25 (C-8), 132.28 (C-14), 128.90 (C-13), 128.35 (C-7), 127.46 (C-Ar), 126.21 (C-Ar), 122.57 (C-12), 95.28 (C-21), 81.41 (C-3), 69.67 (C-15), 69.50(C-19), 66.81 (C-17), 57.87 (C-9), 49.30 (C-5), 37.14 (C-4), 36.30 (C-10), 36.05 (C-1), 25.64 (C-2), 22.38 (C-6), 21.21 (C-29-OAc), 21.02 (C-18), 15.90 (C-20). HRMS (ESI) m/z calcd for $C_{29}H_{34}O_6Na$ $[M + Na]^+$ 501.2253, found 501.2256.

*4.1.8. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl Benzoate (**8a**).* To a stirred solution of **6** (200 mg, 0.46 mmoL) in CH_2Cl_2 (10 mL) were added 4-dimethylaminopyridine (DMAP) (28.09 mg, 0.23 mmoL), 1-ethyl-3-(3-dimethyl amino propyl) carbodiimide (EDC) (142.82 mg, 0.92 mmoL), and benzoic acid (56 mg, 0.46 mmoL) at room temperature for 2 h. The progress of the reaction was checked with TLC. After the stirring was continued at room temperature for 2 h, the reaction mixture was quenched with $NaHCO_3$ (aq.) (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/hexane) to afford the corresponding product **8a** as a white solid (211 mg, 85%). All other derivatives (**8b** to **8y**) were synthesized by following the procedure given for compound **8a** but changing the different types of substituted acid source for EDC coupling of compound **6** at C-17 position. **8a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 1H) , 7.36 (Ar-H, m, 6H), 6.77 (Ar-H, dd, J = 15.6, 10.7 Hz, 2H), 6.20 (H-14, d, J = 15.8 Hz, 1H), 5.99 (H-7, s, 1H), 5.78 (H-21, s, 1H), 4.74 (H-15 s, 2H), 4.57 (H-17a, d, J = 12.6 Hz, 1H), 4.38 (H-17b, d, J = 11.3 Hz, 1H), 4.12 (H-19a, dd, J = 14.3, 7.1 Hz, 1H), 3.75−3.66 (H-19b, H-3, m, 2H), 2.70 (H-9, d, J = 9.8 Hz, 1H), 2.47−2.30 (H-6, m, 2H), 1.98−1.87 (H-2, m, 2H), 1.80 (H-1, dd, J = 21.3, 6.0 Hz, 2H), 1.71 (H-5, dd, J = 14.4, 10.8 Hz, 1H), 1.50 (H-18, s, 3H), 1.07 (H-20, s, 3H). 13C NMR (101 MHz, CDCl3) δ 172.02 (C-16), 166.14 (C-28), 143.44 (C-11), 138.95 (C-Ar), 135.24 (C-8), 132.96 (C-14), 129.57 (C-13), 128.86 (C-7), 128.41 (C-Ar), 128.32 (C-Ar), 127.27 (C-Ar), 126.24 (C-Ar), 122.70 (C-12), 95.30 (C-21), 81.44 (C-3), 69.60(C-15), 69.52 (C-19), 67.24 (C-9), 57.94 (C-5), 49.41 (C-17), 37.19 (C-4), 36.35 (C-10), 36.14 (C-1), 25.67 (C-2), 22.42 (C-6), 21.27 (C-18), 15.96 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{46}O_6Na$ $[M + Na]^+$ 563.2410, found 563.2407.

*4.1.9. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Methoxybenzoate (**8b**).* The title compound **8b** was obtained following the procedure described for **8a**. Yield: 90%. ^{1}H NMR (400 MHz, CDCl3) δ 7.56 (Ar-H, d, J = 7.2 Hz, 1H), 7.50−7.43 (Ar-H, m, 3H), 7.31 (Ar-H, d, J = 7.4 Hz, 5H), 7.02 (H-14, s, 1H), 6.71 (H-11, dd, J = 14.7,10.4 Hz,1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.93 (H-7, s, 1H), 5.73 (H-21, s, 1H), 4.71 (H-15, s, 2H), 4.63 (H-17a, d, J = 12.6 Hz, 1H), 4.53 (H-17b, d, J = 12.6 Hz, 1H), 4.33 (H-19a, d, J = 11.2 Hz, 1H), 4.11−4.03 (H-19b,H-3, m, 2H), 3.80 (H-OCH_3, s, 3H), 2.64 (H-9, d, J = 11.2 Hz, 1H), 2.36 (H-6, dd, J = 22.5, 9.6 Hz, 2H), 2.23 (H-2, d, J = 19.3 Hz, 2H), 1.91−1.86 (H-1, m, 2H), 1.80−1.76 (H-1, m, 1H), 1.45 (H-18, s, 3H), 1.02 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.04 (H-16), 171.17 (H-28), 165.99 (C-Ar), 159.57 (C-Ar), 143.47 (C-11), 138.88 (C-Ar), 135.21 (C-8), 132.35 (C-14), 131.61 (C-13), 129.43 (C-Ar), 128.89 (C-7), 128.34 (C-Ar), 127.23 (C-Ar), 126.21 (C-Ar), 122.69 (C-12), 95.29 (C-21), 81.42 (C-3), 69.62 (C-15),69.51 (C-19), 67.33 (C-9), 60.41 (C-5), 55.48 (C-OCH3), 49.32 (C-17), 37.15 (C-4), 36.33 (C-10), 36.11 (C-1), 25.64 (C-2), 22.66 (C-6), 21.23 (C-18), 15.96 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{38}O_7Na$ $[M + Na]^+$ 593.2515, found 593.2520.

*4.1.10. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Fluorobenzoate (**8c**).* The title compound **8c** was obtained following the procedure described for **8a**. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (Ar-H, d, J = 7.7 Hz, 1H), 7.62 (Ar-H, d, J = 9.3 Hz, 1H), 7.43 (Ar-H, d, J = 6.6 Hz, 4H), 7.29 (Ar-H, s, 3H), 7.03 (H-14, s, 1H), 6.72 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.15 (H-12, d, J = 15.7 Hz, 1H), 5.94 (H-7, s, 1H), 5.72 (H-21, s, 1H), 4.71 (H-15 s, 2H), 4.52 (H-17a, d, J = 12.5 Hz, 1H), 4.32 (H-17b, d, J = 11.3 Hz, 1H), 4.06 (H-19a, dd, J = 14.3, 7.1 Hz, 1H), 3.67−3.61 (H-19b, H-3 m, 2H), 2.63 (H-9, d, J = 10.8 Hz, 1H), 2.35 (H-6, dd, J = 12.9, 7.9 Hz, 2H), 2.23 (H-2, d, J = 17.4 Hz, 2H), 1.85 (H-1, d, J = 14.3 Hz, 2H), 1.80−1.76 (H-5, m, 1H), 1.44 (H-18, s, 3H), 1.00 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.04 (C-16), 165.02 (C-28), 163.52 (C-Ar-F), 143.65 (C-11), 138.84 (C-Ar), 135.18 (C-8), 132.15 (C-14), 130.14 (C-13), 130.08 (C-Ar), 128.38 (C-Ar), 127.71 (C-7), 126.21 (C-Ar), 125.34 (C-Ar), 122.75 (C-12), 120.16 (C-Ar), 119.99 (C-Ar), 95.30 (C-21), 81.40 (C-3), 69.64 (C-15), 69.51 (C-19), 67.65 (C-9), 57.84 (C-5), 49.28 (C-17), 37.13 (C-4), 36.32 (C-10), 36.12 (C-1), 25.65 (C-2), 22.41 (C-6), 21.22 (C-18), 15.97 (C-20). HRMS (ESI) m/z calcd for $C_{34}H_{35}O_6FNa$ $[M + Na]^+$ 581.2315, found 581.2317.

*4.1.11. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Chlorobenzoate (**8d**).* The title compound **8d** was obtained following the procedure described for **8a**. Yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.85 (Ar-H, m, 2H), 7.52 (Ar-H, dd, J = 16.5, 7.3 Hz, 3H), 7.37 (Ar-H, dt, J = 15.5, 7.9 Hz, 4H), 7.10 (H-14, s, 1H), 6.78 (H-11, dd, J = 15.6, 10.6 Hz, 1H), 6.21 (H-12, d, J = 15.7 Hz, 1H), 5.99 (H-7, s, 1H), 5.78 (H-21, s, 1H), 4.78 (H-15, s, 2H), 4.60 (H-17a, d, J = 12.5 Hz, 1H), 4.38 (H-17b, d, J = 11.3 Hz, 1H), 4.12 (H-19a, dd, J = 14.2, 7.1 Hz, 1H), 3.69 (H-19b, H-3, dd, J = 13.3, 7.4 Hz, 2H), 2.68 (H-9, d, J = 12.0 Hz, 1H), 2.43 (H-6, dd, J = 14.0, 11.7 Hz, 2H), 2.29 (H-2 d, J = 16.5 Hz, 2H), 1.91 (H-1, dd, J = 32.1, 16.3 Hz, 2H), 1.74 (H-5, dd, J = 8.8, 4.2 Hz, 1H), 1.50 (H-18, s, 3H), 1.07 (H-20, s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 171.96 (C-16), 164.90 (C-28), 143.57 (C-11), 138.88 (C-Ar), 135.19 (C-8), 134.49 (C-Ar), 132.98 (C-14), 132.18 (C-Ar), 132.07 (C-Ar), 129.78 (C-Ar), 129.57 (C-13), 128.89 (C-27), 128.85 (C-7), 128.34 (C-Ar), 127.75 (C-Ar), 127.74 (C-Ar), 126.20 (C-Ar), 122.76 (C-12), 95.29 (C-21), 81.40 (C-3), 69.60 (C-15), 69.50 (C-19), 67.67 (C-9), 57.86 (C-5), 49.31 (C-17), 37.13 (C-4), 36.33 (C-10), 36.14 (C-1), 25.64 (C-2), 22.42 (C-6), 21.23 (C-18), 14.12 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{46}O_6Na$ $[M + Na]^+$ 597.2020, found 597.2022.

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*4.1.12. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Bromobenzoate (**8e**).* The title compound **8e** was obtained following the procedure described for **8a**. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (Ar-H, s, 1H), 7.97 (Ar-H, d, J = 8.0 Hz, 1H), 7.71 (Ar-H, d, J = 6.9 Hz, 1H), 7.52 (Ar-H, d, J = 6.4 Hz, 2H), 7.39−7.35 (Ar-H, m, 4H), 7.13 (H-14, s, 1H), 6.80 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.23 (H-12, d, J = 15.7 Hz, 1H), 6.01 (H-7, s, 1H), 5.80 (H-21, s, 1H), 4.80 (H-15, s, 2H), 4.62 (H-17a, d, J = 12.6 Hz, 1H), 4.40 (H-17b, d, J = 11.2 Hz, 1H), 4.14 (H-19a, q, J = 7.2 Hz, 1H), 3.77−3.69 (H-19b, H-3, m, 2H), 2.70 (H-9, d, J = 11.2 Hz, 1H), 2.43 (H-6, dd, J = 26.6, 13.6 Hz, 2H), 2.36−2.27 (H-2, m, 2H), 1.98 (H-1, d, J = 13.7 Hz, 2H), 1.86 (H-5, dd, J = 13.5, 3.1 Hz, 1H), 1.52 (H-18, s, 3H), 1.08 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.00 (C-16), 164.79 (C-28), 143.64 (C-11), 138.87 (C-Ar), 135.90 (C-8), 135.18 (C-Ar), 132.49 (C-14), 132.26 (C-Ar), 132.16 (C-Ar), 130.06 (C-13), 128.90 (C-7), 128.82 (C-Ar), 128.35 (C-Ar), 128.21 (C-Ar), 127.75 (C-Ar), 126.21 (C-Ar), 122.77, 95.29 (C-21), 81.40 (C-3), 69.63 (C-15), 69.49 (C-19), 67.70 (C-19), 57.83 (C-5), 49.29 (C-17), 37.12 (C-4), 36.33 (C-10), 36.13 (C-1), 25.63 (C-1), 22.42 (C-6), 21.23 (18), 15.94 (C-20). HRMS (ESI) m/z calcd for $C_{34}H_{34}O_6Br$ $[M + Na]^+$ 641.1515, found 641.1512.

*4.1.13. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Iodobenzoate (**8f**).* The title compound **8f** was obtained following the procedure described for **8a**. Yield: 94%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (Ar-H, s, 1H), 8.01 (Ar-H, d, J = 7.8 Hz, 1H), 7.91 (Ar-H, d, J = 7.9 Hz, 1H), 7.52 (Ar-H, d, J = 7.0 Hz, 2H), 7.43−7.33 (Ar-H, m, 3H), 7.22 (Ar-H, t, J = 7.8 Hz, 1H), 7.13 (H-14, s, 1H), 6.80 (H-11, dd, J = 15.6, 10.7 Hz, 1H), 6.23 (H-12, d, J = 15.7 Hz, 1H), 6.03−5.98 (H-7, s, 1H), 5.80 (H-21, s, 1H), 4.81 (H-15, s, 2H), 4.71 (H-17a, d, J = 12.5 Hz, 1H), 4.62 (H-17b, d, J = 12.5 Hz, 1H), 4.40 (H-19a, d, J = 11.3 Hz, 1H), 3.72 (H-19b, H-3, dd, J = 13.3, 7.5 Hz, 2H), 2.70 (H-9, d, J = 10.6 Hz, 1H), 2.43 (H-6, dd, J = 26.7, 12.2 Hz, 2H), 1.98 (H-2, dd, J = 37.5, 22.8 Hz, 2H), 1.89−1.77 (H-1, m, 2H), 1.73−1.66 (H-5, m, 1H), 1.52 (H-18, s, 3H), 1.09 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.02 (C-16), 164.63 (C-28), 143.70 (C-11), 141.78 (C-Ar), 138.86 (C-Ar), 138.38 (C-Ar), 135.17 (C-8), 132.21 (C-14), 132.16 (C-13), 130.18 (C-Ar), 128.92 (C-Ar), 128.80 (C-7), 128.68 (C-Ar), 128.37 (C-Ar), 127.71 (C-Ar), 126.21 (C-Ar), 122.77 (C-12), 95.30 (C-21), 81.40 (C-3), 69.65 (C-15), 69.50 (C-19), 67.69 (C-9), 57.81 (C-5), 49.26 (C-17), 37.11 (C-4), 36.33 (C-10), 36.13 (C-1), 25.64 (C-2), 22.42 (C-6), 21.23 (C-18), 15.96 (C-20). HRMS (ESI) m/z calcd for $C_{34}H_{35}O_6I$ $[M + Na]^+$ 689.1376, found 689.1379.

*4.1.14. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl Furan-3-carboxylate (**8 g**).* The title compound **8g** was obtained following the procedure described for **8a**. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (Ar-H, furan, s, 1H), 7.52 (Ar-H, d, J = 7.8 Hz, 2H), 7.45 (Ar-H, s, 1H), 7.43−7.30(Ar-H, m, 3H), 7.14 (H-14, s, 1H), 6.84−6.76 (H-11, m, 1H), 6.22 (d, J = 15.7 Hz, 1H), 5.97 (H-7, s, 1H), 5.80 (H-21, s, 1H), 4.81 (H-15, s, 2H), 4.66 (H-17a, d, J = 12.6 Hz, 1H), 4.49 (H-17b, d, J = 12.6 Hz, 1H), 4.39 (H-19a d, J = 11.3 Hz, 1H), 3.76−3.67 (H-19b, H-3, m, 2H), 2.68 (H-9, d, J = 10.1 Hz, 1H), 2.50−2.26 (H-6, m, 2H), 1.94 (H-2, dd, J = 15.1, 14.5 Hz, 2H), 1.88−1.73 (H-1 m, 2H), 1.71−1.64 (H-5, m, 1H), 1.51 (H-18, s, 3H), 1.07 (H-20s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.09 (C-16), 162.72 (C-28), 147.78 (C-Furan), 143.77 (C-11), 138.87 (C-Ar), 135.21 (C-8), 132.27 (C-14), 128.91 (C-13), 128.87 (C-7), 128.36 (C-Ar), 127.44 (C-Ar), 126.21 (C-Ar), 122.69 (C-12), 119.37 (C-Furan), 109.79 (C-Furan), 95.29 (C-21), 81.41 (C-3), 69.65 (C-15), 69.50 (C-19), 66.63 (C-9), 57.94 (C-5), 49.31 (C-17), 37.14 (C-4), 36.32 (C-10), 36.09 (C-1), 25.64 (C-2), 22.39 (C-6), 21.23 (C-18), 15.92 (C-20). HRMS (ESI) m/z calcd for $C_{32}H_{34}O_7$ $[M + Na]^+$ 553.2202, found 553.2204.

*4.1.15. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-(Trifluoromethyl)benzoate (**8h**).* The title compound **8h** was obtained following the procedure described for **8a**. Yield: 95%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (Ar-H, s, 1H), 7.76 (Ar-H, d, J = 7.7 Hz, 1H), 7.55 (Ar-H, d, J = 7.8 Hz, 1H), 7.44 (Ar-H, d, J = 7.6 Hz, 3H), 7.30 (Ar-H, d, J = 7.4 Hz, 3H), 7.03 (H-14, s, 1H), 6.75(H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.94 (H-7, s, 1H), 5.72 (H-21, s, 1H), 4.71 (H-15, s, 2H), 4.66 (17a, d, J = 12.7 Hz, 1H), 4.59 (H-17b, d, J = 12.5 Hz, 1H), 4.31 (19a, d, J = 11.3 Hz, 1H), 3.68−3.63 (H-19b, H-3, m, 2H), 2.63 (H-9, d, J = 10.9 Hz, 1H), 2.35 (H-6, dt, J = 12.7, 10.4 Hz, 2H), 2.24 (H-2, d, J = 18.2 Hz, 2H), 2.05−1.93 (H-1, m, 2H), 1.79 (H-1, d, J = 3.1 Hz, 1H), 1.44 (H-18, s, 3H), 1.00 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.02 (C-16), 164.81 (C-28), 143.78 (C-11), 138.84 (C-Ar), 135.15 (C-8), 132.87 (C-14), 132.08 (C-Ar), 131.15 (C-Ar), 131.09 (C-Ar), 130.82 (C-Ar), 129.48 (C-13), 129.20 (C-Ar), 128.93 (C-7), 128.73 (C-Ar), 128.38 (C-Ar), 127.93 (C-Ar), 126.40 (C-Ar), 126.22 (C-CF3), 122.83 (C-Ar), 95.30 (C-21), 81.38 (C-3), 69.63 (C-15), 69.49 (C-19), 67.85 (C-9), 57.83 (C-5), 49.25 (C-17), 37.10 (C-4), 36.32 (C-10), 36.14 (C-1), 25.63 (C-2), 22.43 (C-6), 21.22 (C-18), 15.94 (C-120). HRMS (ESI) m/z calcd for $C_{35}H_{35}O_6$ $[M + Na]^+$ 631.2283, found 631.2276.

*4.1.16. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Methylbenzoate (**8i**).* The title compound **8i** was obtained following the procedure described for **8a**. Yield: 88%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (Ar-H, s, 1H), 8.75−8.61 (Ar-H, m, 2H), 7.43 (Ar-H, d, J = 6.6 Hz, 2H), 7.33−7.24(Ar-H, m, 4H), 7.06 (H-14, s, 1H), 6.71 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.15 (H-12, d, J = 15.7 Hz, 1H), 5.98 (H-7, s, 1H), 5.71 (H-21, s, 1H), 4.73 (H-15,H-17a, d, J = 15.4 Hz, 3H), 4.63 (H-17b, d, J = 12.4 Hz, 1H), 4.30 (H-19a, d, J = 11.3 Hz, 1H), 3.63 (H-19b, H-3, dd, J = 11.5, 6.8 Hz, 2H), 2.65 (H-9, d, J = 10.1 Hz, 1H), 2.41−2.21 (H-6, m, 2H), 1.90 (H-2, dd, J = 35.1, 20.8 Hz, 2H), 1.72 (H-1, dd, J = 31.7, 8.7 Hz, 2H), 1.65 (H-5, s, 1H), 1.42 (H-18, CH3-Ar-H,s, 6H), 0.99 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.99 (C-16), 163.49 (C-28), 147.67 (C-Ar), 146.24 (C-Ar), 144.58 (C-Ar), 143.84 (C-11), 138.84 (C-Ar), 134.99 (C-8), 131.69 (C-14), 128.92 (C-13), 128.74 (C-7), 128.66 (C-Ar), 128.37 (C-Ar), 126.21 (C-Ar), 122.94 (C-12), 95.28 (C-21), 81.37 (C-3), 69.65 (C-15), 69.49 (C-9), 68.40 (C-9), 57.77 (C-5), 49.17 (C-17), 37.09 (C-4), 36.30 (C-10),

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36.11 (C-1), 29.72 (C-Ar-CH3) 25.63 (C-2), 22.45 (C-6), 21.21 (C-18), 15.97 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{38}O_6$ $[M + Na]^+$ 577.2566, found 577.2564.

*4.1.17. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3,5-Dimethoxybenzoate (**8j**).* The title compound **8j** was obtained following the procedure described for **8a**. Yield: 92%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.48 (H-Ar, m, 2H), 7.40−7.34 (H-Ar, m, 3H), 7.16 (H-Ar, C-17-Ester, d, J = 2.4 Hz, 2H), 7.09 (H-14, d, J = 1.8 Hz, 1H), 6.75 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.65 (H-Ar, C-17-Ester,dd, J = 4.6, 2.3 Hz, 1H), 6.21 (H-12, d, J = 15.7 Hz, 1H), 5.99−5.95 (H-7, m, 1H), 5.78 (H-21, s, 1H), 4.77 (H-15, d, J = 1.2 Hz, 2H), 4.67 (H-17a, d, J = 12.7 Hz, 1H), 4.57 (H-17b, d, J = 12.6 Hz, 1H), 4.37 (H-19a, d, J = 11.4 Hz, 1H), 3.84 (H-OCH_3x2, s, 6H), 3.69 (H-19b, H-3, m, 2H), 2.68 (H-9, d, J = 10.7 Hz, 1H), 2.46−2.27 (H-6, m, 2H), 1.97−1.83 (H-2, m, 2H), 1.79−1.63 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 1.04 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.13 (C-16), 165.89 (C-28), 160.64 (C-Ar), 143.60 (H-11), 138.85 (C-Ar), 135.17 (C-8), 132.28 (C-14), 132.17 (C-Ar), 128.93 (C-13), 128.84 (C-7), 128.38 (C-Ar) , 127.22 (C-Ar), 126.22 (C-Ar), 122.71 (C-12), 107.30 (C-Ar) , 105.27 (C-Ar), 95.29 (C-21), 81.41 (C-3), 69.68 (C-15), 69.52 (C-19), 67.43 (C-17), 57.77 (C-9) , 55.64 (C-Ar-OCH_3), 49.26 (C-5), 37.12 (C-4), 36.32 (C-10), 36.09 (C-1), 25.63 (C-2), 22.38 (C-6), 21.22 (C-18), 15.97 (C-20). HRMS (ESI) m/z calcd for $C_{36}H_{40}O_8$ $[M + Na]^+$ 623.2621, found 623.2613.

*4.1.18. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3,4,5-Trimethoxybenzoate (**8k**).* The title compound **8 k** was obtained following the procedure described for **8a**. Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (H-Ar, m, 2H), 7.40−7.34 (H-Ar, m, 3H), 7.27 (H-Ar, C-17-Ester, d, J = 4.4 Hz, 2H), 7.10 (H-14, d, J = 1.6 Hz, 1H),6.79 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.22 (H-12, d, J = 15.7 Hz, 1H), 5.98−5.94 (H-7, m, 1H), 5.78 (H-21, s, 1H), 4.78 (H-15, s, 2H), 4.63 (H-17a, H-17b, dd, J = 38.3, 12.8 Hz, 2H), 4.37 (H-19a, d, J = 11.3 Hz, 1H), 3.92 (H-OCH_3x2, s, 6H), 3.91 (H-OCH_3, s, 3H), 3.72−3.65 (H-19b, H-3, m, 2H), 2.68 (H-9, d, J = 10.6 Hz, 1H), 2.36 (H-6, m, 2H), 1.92 (H-2, m, 2H), 1.81−1.67 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 1.06 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.07 (C-16), 165.81 (C-28), 152.95 (C-Ar), 143.5 (C-11), 138.82 (C-Ar), 135.25 (C-8), 132.28 (C-14), 128.94 (C-13), 128.84 (C-7), 128.38 (C-Ar), 126.76 (C-Ar), 126.21 (C-Ar), 125.28 (C-Ar) , 122.67 (C-12), 106.82 (C-Ar), 95.30 (C-21), 81.39 (C-3), 69.67 (C-15), 69.49 (C-19), 67.11 (C-17), 60.97 (C-OCH3), 57.91 (C-9), 56.32 (C-OCH3), 49.31 (C-5), 37.12 (C-4), 36.32 (C-10), 36.13 (C-1), 25.64 (C-2), 22.39 (C-6), 21.21 (C-18), 15.92 (20). HRMS (ESI) m/z calcd for $C_{37}H_{43}O_9$ $[M + H]^+$ 631.2907, found 631.2910.

*4.1.19. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 3-Chloro-4-methoxybenzoate (**8l**).* The title compound **8l** was obtained following the procedure described for **8a**. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (H-Ar, C-17-ester, d, J = 2.1 Hz, 1H), 7.93 (H-Ar, C-17-Ester , dd, J = 8.6, 2.1 Hz, 1H), 7.52−7.48(H-Ar, m, 2H), 7.39−7.33 (H-Ar, m, 3H), 7.12 (H-14, s, 1H), 6.97 (H-Ar, C-17-Ester, d, J = 8.7 Hz, 1H), 6.78 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.21 (H-12, d, J = 15.7 Hz, 1H), 5.98 (H-7, s, 1H), 5.78 (H-21, s, 1H), 4.79 (H-15, s, 2H), 4.61 (H-17a, H-17b, dd, J = 43.3, 12.5 Hz, 2H), 4.38 (H-19b, d, J = 11.2 Hz, 1H), 3.97 (H-OCH_3, s, 3H), 3.69 (H-19b, H-3, dd, J = 11.7, 7.6 Hz, 2H), 2.68 (H-9, d, J = 10.2 Hz, 1H), 2.43−2.26 (H-6, m, 2H), 1.97−1.84 (H-2, m, 2H), 1.73 (H-1, H-5, m, 3H), 1.50 (H-18, s, 3H), 1.06 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.10 (C-16), 164.91 (C-28), 158.64 (C-Ar), 143.67 (C-11), 138.85 (C-Ar), 135.22 (C-8), 132.32 (C-14), 131.52 (C-Ar), 129.99 (C-13), 128.93 (C-7), 128.82 (C-Ar), 128.37 (C-Ar), 127.48 (C-Ar), 126.21 (C-Ar), 123.43 (C-Ar), 122.70 (C-12), 122.39 (C-Ar), 111.30 (C-Ar), 95.29 (C-21), 81.41 (C-3), 69.67 (C-15), 69.51 (C-19), 67.36 (C-17), 57.86 (C-9), 56.39 (C-OCH3), 49.27 (C-5), 37.11 (C-4), 36.32 (C-10), 36.11 (C-1), 25.64 (C-2), 22.40 (C-6), 21.23 (C-18), 15.97 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{38}O_7Cl$ $[M + H]^+$ 605.2306, found 605.2304.

*4.1.20. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 4-Bromo-2-fluorobenzoate (**8m**).* The title compound **8 m** was obtained following the procedure described for **8a**. Yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (H-Ar- C-17-Ester, dd, J = 6.3, 2.6 Hz, 1H), 7.62 (H-Ar-C-17-Ester, ddd, J = 8.8, 4.2, 2.6 Hz, 1H), 7.52−7.46 (H-Ar, m, 2H), 7.40−7.33 (H-Ar , m, 3H), 7.15 (H-14, d, J = 1.6 Hz, 1H), 7.09−7.01 (H-Ar-C-17-Ester, m, 1H), 6.77 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.23 (H-12, d, J = 15.7 Hz, 1H), 6.04−5.98 (H-7, m, 1H), 5.78 (H-21, s, 1H), 4.80 (H-15, J = 1.6, 2H), 4.65 (H-17a, H-17b, q, J = 12.5 Hz, 2H), 4.37 (H-19a, d, J = 11.5 Hz, 1H), 3.73−3.65 (H-19b, H-3, m, 2H), 2.68 (H-9, d, J = 10.3 Hz, 1H), 2.39 (H-6, m, 2H), 1.98−1.84 (H-2, m, 2H), 1.79−1.64 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 1.05 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.07 (C-16), 162.75 (C-28), 159.63 (C-Ar), 143.72 (C-11), 138.85 (C-Ar), 137.29 (C-Ar), 137.20 (C-Ar), 135.05 (C-8), 134.70 (C-Ar), 131.89 (C-14), 128.92 (C-13), 128.83 (C-7), 128.37 (C-Ar), 128.05 (C-Ar), 126.22 (C-Ar), 122.90 (C-12), 119.06 (C-Ar), 118.82 (C-Ar0, 116.48 (C-Ar), 95.30 (C-21), 81.40 (C-3), 69.67 (C-15), 69.51 (C-19), 68.13 (C-17), 57.65 (C-9), 49.23 (C-5), 37.11 (C-4), 36.32 (C-10), 36.07 (C-1), 25.62 (C-2), 22.43 (C-6), 21.23 (C-18), 15.94 (20). HRMS (ESI) m/z calcd for $C_{34}H_{34}BrFO_6$ $[M + Na]^+$ 659.1420, found 659.1414.

*4.1.21. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(Trifluoromethyl)benzoate (**8n**).* The title compound **8n** was obtained following the procedure described for **8a**. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (H-Ar, C-17-Ester, d, J = 8.4 Hz, 2H), 7.62 (H-Ar, C-17-Ester , dd, J = 5.9, 3.1 Hz, 2H), 7.53−7.48(H-Ar, m, 2H), 7.36 (H-Ar, m, 3H), 7.16 (H-14, s, 1H), 6.74 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.21 (H-12, t, J = 12.4 Hz, 1H), 6.02 (H-7, s, 1H), 5.78 (H-21, s, 1H), 4.81 (s, 2H), 4.63 (H-17a, H-17b, dd, J = 39.3, 12.3 Hz, 2H), 4.37 (H-19a, d, J = 11.4 Hz, 1H), 3.68(H-19b, H-3, m, 3H), 2.68 (H-9, d, J = 10.5 Hz, 1H), 2.46−2.24 (H-6, m, 2H), 1.91 (H-2, m, 2H), 1.80−1.65 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 1.04 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.17 (16), 166.36 (C-28), 143.72 (C-11), 138.85 (C-Ar), 135.03 (C-8), 131.84 (C-14), 131.75 (C-Ar), 131.20 (C-Ar), 130.28 (C-Ar), 128.93 (C-13), 128.84 (C-7), 128.69 (C-Ar), 128.37 (C-Ar), 126.73 (C-Ar),

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126.68 (C-Ar), 126.22 (C-Ar), 122.91 (C-12), 95.30 (C-21), 81.40 (C-3), 69.70 (C-15), 69.53 (C-19), 68.46 (C-17), 57.60 (C-9), 49.22 (C-5), 37.14 (C-4), 36.28 (C-10), 36.08 (C-1), 25.65 (C-2), 22.45 (C-6, 21.21 (C-18), 15.93 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{35}F_3O_6$ $[M + Na]^+$ 631.2283, found 631.2286.

*4.1.22. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-Phenylacetate (**8o**).* The title compound **8o** was obtained following the procedure described for **8a**. Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (Ar-H, d, J = 7.5 Hz, 2H), 7.35−7.24 (Ar-H, m, 8H), 6.99 (H-14, s, 1H), 6.61 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 5.96 (H-12, d, J = 15.7 Hz, 1H), 5.81 (H-7, s, 1H), 5.74 (H-21, s, 1H), 4.73 (H-15, s, 2H), 4.41 (H-17a, d, J = 12.5 Hz, 1H), 4.30 (H-17b, H-19a, 19b, t, J = 11.2 Hz, 2H), 3.64 (H-19b, H-3 dd, J = 12.1, 7.8 Hz, 2H), 3.57 (CH_2-Phenyl, s, 2H), 2.48 (H-9,d, J = 10.3 Hz, 1H), 2.42−2.15 (H-6, m, 2H), 1.82 (H-6, dd, J = 30.8, 15.5 Hz, 2H), 1.70−1.51 (H-1, H-5, m, 3H), 1.45 (H-18, s, 3H), 0.96(H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.18 (C-16), 171.13 (C-28), 143.69 (C-11), 138.86 (C-Ar), 135.03 (C-8), 134.21 (C-Ar), 132.20 (C-14), 129.42 (C-13), 128.94 (C-7), 128.79 (C-Ar), 128.55 (C-Ar), 128.38 (C-Ar), 127.82 (C-Ar), 127.09 (C-Ar), 126.22 (C-Ar), 122.64 (C-12), 95.29 (C-21), 81.42 (C-3), 69.67 (C-15), 69.51 (C-19), 67.30 (s), 57.55 (C-5), 49.24 (C-17), 41.51 (C-CH_2-Phenyl), 37.12 (C-4), 36.29 (C-10), 35.97 (C-1), 25.66 (C-2), 22.36 (C-6), 21.21 (C-18), 15.89 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{38}O_6$ $[M + Na]^+$ 577.2566, found 577.2569.

*4.1.23. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(4-Fluorophenyl)acetate (**8p**).* The title compound **8p** was obtained following the procedure described for **8a**. Yield: 95%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.47 (H-Ar, m, 2H), 7.40−7.33 (H-Ar, m, 3H),7.27−7.21 (H-Ar, m, 2H), 7.08 (H-14, s, 1H), 7.03−6.97 (H-Ar, m, 2H), 6.68 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.05 (H-12, d, J = 15.7 Hz, 1H), 5.88−5.83 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.79 (H-15, d, J = 1.7 Hz, 2H), 4.37 (H-17a, H-17b, H-19a, dt, J = 12.2, 11.1 Hz, 3H), 3.71−3.64 (H-19b, H-3, m, 2H), 3.58 (H-29, s, 2H), 2.52 (H-9, d, J = 10.6 Hz, 1H), 2.43−2.19 (H-6, m, 2H), 1.86 (H-2, m, 2H), 1.73 (H-1, H-15, m, 3H), 1.49 (H-18, s, 3H), 0.99 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.15 (C-16), 171.06 (C-28), 163.19 (C-Ar), 160.75 (C-Ar), 143.67 (C-11), 138.84 (C-Ar), 135.12 (C-8), 132.12 (C-14), 131.00 (C-Ar), 130.92 (C-13), 128.93 (C-7), 128.78 (C-Ar), 128.37 (C-Ar), 127.97 (C-Ar), 126.22 (C-Ar), 122.61 (C-12), 115.46 (C-Ar), 115.24 (C-Ar), 95.29 (C-21), 81.39 (C-3), 69.67 (C-15), 69.49 (C-19), 67.35 (C-17), 57.74 (C-9), 49.28 (C-5), 40.53 (C-CH2-Phenyl), 37.12 (C-4), 36.29 (C-10), 36.02 (C-1), 25.65 (C-2), 22.39 (C-6), 21.20 (C-18), 15.85 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{37}FO_6$ $[M + Na]^+$ 595.2472, found 595.2470.

*4.1.24. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(4-Chlorophenyl)acetate (**8q**).* The title compound **8q** was obtained following the procedure described for **8a**. Yield: 89%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (H-Ar, m, 2H), 7.39−7.35 (H-Ar, m, 3H), 7.31−7.26 (H-Ar, m, 2H), 7.23 (H-Ar, dd, J = 5.8, 3.6 Hz, 2H), 7.12 (H-14, t, J = 1.8 Hz, 1H), 6.66 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.06 (H-12, d, J = 15.7 Hz, 1H), 5.90−5.85 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.80 (H-15, d, J = 1.6 Hz, 2H), 4.47−4.32 (H-17a, H-17b, H-19a, m, 3H), 3.76 (H-29, d, J = 2.4 Hz, 2H), 3.72−3.64 (H-19b, H-3, m, 2H), 2.53 (H-9, d, J = 10.5 Hz, 1H), 2.41−2.19 (H-6, m, 2H), 1.92−1.78 (H-2, m, 2H), 1.70(H-1, H-5, m, 3H), 1.49 (H-18, s, 4H), 0.99 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.20 (C-16), 170.15 (C-28), 143.61 (H-11), 138.86 (C-Ar), 135.12 (C-8), 134.53 (C-Ar), 132.56 (C-14), 132.12 (C-Ar), 131.70 (C-Ar), 129.45 (C-13), 128.91 (C-7), 128.71 (C-Ar), 128.37 (C-Ar), 127.85 (C-Ar), 126.94 (C-Ar), 126.22 (C-Ar), 122.67 (C-12), 95.30 (C-21), 81.43 (C-3), 69.68 (C-15), 69.52 (C-19), 67.43 (C-17), 57.59 (C-9), 49.26 (C-5), 39.21 (C-CH2-Phenyl), 37.14 (C-4), 36.29 (C-10), 35.99 (C-1), 25.66 (C-2), 22.37 (C-6), 21.21 (C-18), 15.89 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{38}O_6Cl$ $[M + H]^+$ 589.2357, found 589.2360.

*4.1.25. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(4-Iodophenyl)acetate (**8r**).* The title compound **8r** was obtained following the procedure described for **8a**. Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.62 (H-Ar, m, 2H), 7.50 (H-Ar, dd, J = 7.8, 1.6 Hz, 2H), 7.40−7.33 (H-Ar, m, 3H), 7.07 (H-14, s, 1H), 7.03 (H-Ar, d, J = 8.1 Hz, 2H), 6.67 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.03 (H-12, d, J = 15.7 Hz, 1H), 5.87−5.83 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.80 (H-15, d, J = 1.3 Hz, 2H), 4.37 (H-17a, H-17b, H-19a, dt, J = 12.2, 10.2 Hz, 3H), 3.69 (H-19b, H-3, d, J = 10.3 Hz, 2H), 3.54 (H-29, s, 2H), 2.49 (H-9, d, J = 10.4 Hz, 1H), 2.42−2.19 (H-6, m, 2H), 1.94−1.80 (H-2, m, 2H), 1.76−1.60(H-1, H-5,m, 3H), 1.49 (H-18, s, 3H), 0.98 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.15 (C-16), 170.62 (C-28), 143.76 (C-11), 138.84 (C-Ar), 137.57 (C-Ar), 135.09 (C-8), 133.85 (C-Ar), 132.09 (C-14), 131.48 (C-13), 128.94 (C-7), 128.74 (C-Ar), 128.38 (C-Ar), 128.25 (C-Ar), 126.22 (C-Ar), 122.63 (C-12), 95.30 (C-21), 81.39 (C-3), 69.70 (C-15), 69.49 (C-19), 67.50 (C-17), 57.69 (C-9), 49.28 (C-5), 40.93 (C-CH2-Phenyl), 37.12 (C-4), 36.29 (C-10), 36.01 (C-1), 25.67 (C-2), 22.40 (C-6), 21.20 (C-18), 15.85 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{37}O_6I$ $[M + Na]^+$ 703.1533, found 703.1526.

*4.1.26. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(4-Methoxyphenyl)acetate (**8s**).* The title compound **8s** was obtained following the procedure described for **8a**. Yield: 91%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (H-Ar, m, 2H), 7.39−7.34 (H-Ar, m, 3H), 7.22−7.16 (H-Ar, m, 2H), 7.05 (H-14, s, 1H), 6.86 (H-Ar, t, J = 6.9 Hz, 2H), 6.64 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.02 (H-12, d, J = 15.7 Hz, 1H), 5.85 (H-7, s, 1H), 5.77 (H-21, s, 1H), 4.78 (H-15, s, 2H), 4.36 (H-17a, H-17b, H-19a, dt, J = 15.7, 12.4 Hz, 3H), 3.80 (H-OCH_3, s, 3H), 3.72−3.65 (H-19b, H-3, m, 2H), 3.47 (H-29, s, 2H), 2.52 (H-9, d, J = 9.7 Hz, 1H), 2.29 (H-6,m, 2H), 1.93−1.79 (H-2, m, 2H), 1.77−1.65 (H-1, H-5, m, 3H), 1.50−1.43 (H-18, m, 3H), 0.99 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.19 (C-16) , 171.50 (C-28), 158.65 (C-Ar), 143.61 (C-11), 138.84 (C-Ar), 135.06 (C-8), 132.23 (C-14), 130.40 (C-13), 128.93 (C-7), 128.84 (C-Ar), 128.37 (C-Ar), 127.72 (C-Ar), 126.22 (C-Ar), 122.62 (C-12), 113.93 (C-Ar), 95.30 (C-21), 81.42 (C-3), 69.67 (C-15), 69.51 (C-19), 67.21 (C-17), 57.56 (C-9), 55.32 (C-

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OCH3), 49.26 (C-5), 40.56 (C-CH2-Phenyl), 37.11 (C-4), 36.29 (C-10), 35.99 (C-1), 25.65 (C-2), 22.36 (C-6), 21.20 (C-18), 15.87 (C-20). HRMS (ESI) m/z calcd for $C_{36}H_{40}O_7$ $[M + Na]^+$ 607.2672, found 607.2667.

*4.1.27. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(p-Tolyl)acetate (**8t**).* The title compound **8t** was obtained following the procedure described for **8a**. Yield: 91%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.47 (H-Ar, m, 2H), 7.41−7.32 (H-Ar, m, 3H), 7.16−7.11 (H-Ar, m, 4H), 7.03(H-14, s, 1H), 6.63 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.02 (H-12, d, J = 15.7 Hz, 1H), 5.87−5.83 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.78 (H-15, s, 2H), 4.46−4.28 (H-17a, H-17b, H-19a, m, 3H), 3.72−3.65 (H-19b, H-3, m, 2H), 3.47 (H-29, s, 2H), 2.50 (H-9, d, J = 10.2 Hz, 1H), 2.38 (H-6a, m, 1H), 2.33 (H-CH3-Pheny ester, s, 3H), 2.22 (H-6b, m, 1H), 1.92−1.80 (H-2, m, 2H), 1.75−1.64 (H-1,H-5, m, 3H), 1.49 (H-18, s, 3H), 0.97 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.19 (C-16), 171.37 (C-28), 143.57 (C-11), 138.84 (C-Ar), 136.66 (C-Ar), 135.08 (C-8), 132.22 (C-14), 131.11 (C-13), 129.26 (C-Ar), 129.22 (C-Ar), 128.94 (C-7), 128.87 (C-Ar), 128.38 (C-Ar), 127.71 (C-Ar), 126.22 (C-Ar), 122.63 (C-12), 95.30 (C-21), 81.44 (C-3), 69.67 (C-15), 69.52 (C-19), 67.20 (C-17), 57.52 (C-9), 50.88 (C-CH3-Ar), 49.25 (C-5), 41.06 (C-CH2-Phenyl), 37.11 (C-4), 36.29 (C-10), 35.97 (C-1), 25.66 (C-2), 22.35 (C-6), 21.21 (C-18), 15.88 (C-20). HRMS (ESI) m/z calcd for $C_{36}H_{40}O_6$ $[M + Na]^+$ 591.2723, found 591.2725.

*4.1.28. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(3,4,5-Trimethoxyphenyl)acetate (**8u**).* The title compound **8u** was obtained following the procedure described for **8a**. Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (H-Ar, dd, J = 7.8, 1.5 Hz, 2H), 7.40−7.34 (H-Ar, m, 3H), 7.06 (H-14, s, 1H), 6.68 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.51 (H-Ar, s, 2H), 5.92 (H-12, d, J = 15.7 Hz, 1H), 5.89−5.86 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.78 (H-15, s, 2H), 4.46−4.30 (H-17a, H-17b, H-19a, m, 3H), 3.86 (H-OCH3x2, s, 6H), 3.83 (H-OCH3 s, 3H),3.67 (H-19b,H-3, m, 2H), 3.54 (H-29, s, 1H), 3.47 (H-29, s, 1H), 2.51 (H-9, d, J = 10.0 Hz, 1H), 2.41−2.22 (H-6, m, 2H), 1.86 (H-2, m, 2H), 1.70 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 0.99 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.18 (C-16), 171.10 (C-28), 153.15 (C-Ar), 144.08 (C-11), 138.81 (C-Ar), 136.87 (C-8), 134.82 (C-Ar), 132.27 (C-C-14), 129.88 (C-13), 128.94 (C-7), 128.54 (C-Ar), 128.38 (C-Ar), 127.99 (C-Ar), 126.21 (C-Ar), 122.71 (C-12), 106.37 (C-Ar), 95.29 (C-21), 81.43 (C-3), 69.74 (C-15), 69.47 (C-19), 67.49 (C-17), 60.88 (C-OCH3), 57.74 (C-9), 56.14 (C-OCH3), 49.36 (C-5), 41.70 (C-CH2-Phenyl), 37.16 (C-4), 36.29 (C-10), 36.00 (C-1), 25.67 (C-2), 22.40 (C-6), 21.18 (C-18), 15.86 (C-20). HRMS (ESI) m/z calcd for $C_{38}H_{44}O_9$ $[M + Na]^+$ 667.2883, found 667.2875.

*4.1.29. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl 2-(3,4-Dichlorophenyl)acetate (**8v**).* The title compound **8v** was obtained following the procedure described for **8a**. Yield: 91%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (H-Ar, m, 2H), 7.42−7.34 (H-Ar, m, 6H), 7.1 (H-14, s, 1H), 6.70 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.03 (H-12, d, J = 15.7 Hz, 1H), 5.90−5.86 (H-7, m, 1H), 5.77 (H-21, s, 1H), 4.82 (H-15, d, J = 7.0 Hz, 2H), 4.45−4.31 (H-17a, H-17b, H-19a, m, 3H), 3.68 (H-19b, H-3, dd, J = 12.2, 4.4 Hz, 2H), 3.57 (H-29, s, 2H), 2.49 (H-9, d, J = 10.2 Hz, 1H), 2.34 (H-6, m, 2H), 1.94−1.81 (H-2, m, 2H), 1.74 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 0.99 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.13 (C-16), 170.17 (C-28), 143.83 (C-11), 138.84 (C-Ar), 135.13 (C-8), 134.34 (C-Ar), 132.37 (C-14), 132.04 (C-Ar), 131.39 (C-13), 130.41 (C-Ar), 128.99 (C-7), 128.93 (C-Ar), 128.72 (C-Ar), 128.37 (C-Ar), 126.22 (C-Ar), 122.61 (C-12), 95.29 (C-21), 81.37 (C-3), 69.69 (C-15), 69.47 (C-19), 67.71 (C-17), 57.78 (C-9), 49.28 (C-5), 40.42 (C-CH2-Pheny), 37.10 (C-4), 36.29 (C-10), 36.02 (C-1), 25.64 (C-2), 22.43 (C-6), 21.20 (C-18), 15.82 (C-20). HRMS (ESI) m/z calcd for $C_{35}H_{36}Cl_2O_6$ $[M + Na]^+$ 645.1787, found 645.1783.

*4.1.30. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl Octanoate (**8w**).* The title compound **8w** was obtained following the procedure described for **8a**. Yield: 95%. White liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (H-Ar, dd, J = 7.9, 1.6 Hz, 2H), 7.39−7.32 (H-Ar, m, 3H), 7.18 (H-14, t, J = 1.9 Hz, 1H), 6.71 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.19 (H-12, d, J = 15.7 Hz, 1H), 5.90−5.86 (H-7, s, 1H), 5.77 (H-21, s, 1H), 4.81 (H-15, d, J = 1.7 Hz, 2H), 4.36 (H-17a, H-17b, H-19a, dt, J = 24.1, 12.6 Hz, 3H), 3.73−3.65 (H-19b, H-3 m, 2H), 2.61 (H-9, d, J = 10.5 Hz, 1H), 2.42−2.26 (H-29, H-6, m, 4H) , 1.78−1.64 (H-2, m, 2H), 1.63−1.52 (H-1, H-5, m, 3H), 1.48 (H-18, s, 3H), 1.33−1.26 (H-30, 31, 32, 33, 34, m, 10H), 1.02 (H-20, s, 3H), 0.88 (H-35, t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53 (C-16), 172.10 (C-28), 143.49 (C-11), 138.87 (C-Ar), 135.30 (C-8), 132.39 (C-14), 128.92 (C-13), 128.89 (C-7), 128.34 (C-Ar), 127.00 (C-Ar), 126.21 (C-Ar), 122.56 (C-12), 95.28 (C-21), 81.42 (C-3), 69.66 (C-15), 69.50 (C-19), 66.52 (C-17), 57.78 (C-9), 49.31 (C-5), 37.14 (C-4), 36.30 (C-10), 36.06 (C-1), 34.33 (C-aliphatic ester), 31.69(C-aliphatic ester), 29.12 (C-aliphatic ester), 28.96, 25.64 (C-2), 24.98(C-aliphatic ester), 22.61(C-aliphatic ester), 22.34 (C-6), 21.21 (C-18), 15.90 (C-20), 14.09 (C-35). HRMS (ESI) m/z calcd for $C_{35}H_{46}O_6$ $[M + Na]^+$ 585.3192, found 585.3193.

*4.1.31. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl Decanoate (**8x**).* The title compound **8x** was obtained following the procedure described for **8a**. Yield: 90%. White liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.46 (H-Ar, m, 2H), 7.39−7.30 (H-Ar, m, 3H), 7.18 (H-14, t, J = 1.9 Hz, 1H), 6.71 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.19 (H-12, d, J = 15.7 Hz, 1H), 5.92−5.86 (H-7, m, 1H), 5.77 (H-21, d, J = 6.8 Hz, 1H), 4.81 (H-15, d, J = 1.7 Hz, 2H), 4.36 (H-17a, H-17b, H-19a, m, J = 36.5, 12.7 Hz, 1H), 3.74−3.64 (H-19a, H-3, m, 2H), 2.61 (H-9, d, J = 10.3 Hz, 1H), 2.41−2.26 (H-6, H-29, m, 4H), 1.94−1.78 (H-2, m, 2H), 1.59 (H-1, H-5, m, J = 17.9, 14.4, 7.0 Hz, 3H), 1.49 (H-18, s, 3H), 1.26 (H-30 to H-36, m, 14H), 1.02 (H-20, s, 3H), 0.88 (H-37, t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53 (C-16), 172.09 (C-28), 143.47 (C-11), 138.87 (C-Ar), 135.31 (C-8), 132.39 (C-14), 128.94 (C-13), 128.89 (C-7), 128.34 (C-Ar), 126.97 (C-Ar), 126.21 (C-Ar), 122.56 (C-12), 95.28 (C-21), 81.42 (C-3), 69.65 (C-15), 69.51 (C-19), 66.50 (C-17), 57.79 (C-9), 49.32 (C-5), 37.14 (C-4), 36.30 (C-10), 36.06 (C-1),

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34.34 (C-aliphatic ester), 33.85 (C-aliphatic ester), 31.88 (C-aliphatic ester), 29.46 (C-aliphatic ester), 29.40 (C-aliphatic ester), 29.31 (C-aliphatic ester), 29.28 to 29.07 (C-aliphatic ester), 25.64 (C-2), 24.99−22.67 (C-aliphatic ester), 22.35 (C-6), 21.21 (C-18), 15.90 (C-20), 14.12 (C-37). HRMS (ESI) m/z calcd for $C_{37}H_{50}O_6$ $[M + Na]^+$ 613.3505, found 613.3492.

*4.1.32. ((4aR,6aR,7S,10bR)-6a,10b-Dimethyl-7-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-3-phenyl-4a,5,6,6a,7,10,10a,10b-octahydro-1H-naphtho[2,1-d][1,3]-dioxin-8-yl)methyl Dodecanoate (**8y**).* The title compound **8y** was obtained following the procedure described for **8a**. Yield: 90%. White liquid. ^{1}H NMR δ 7.49 (H-Ar, dt, J = 8.2, 2.2 Hz, 2H), 7.35 (H-Ar, m, 3H), (H-14, t, J = 1.9 Hz, 1H), 6.71 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.19 (H-12, d, J = 15.7 Hz, 1H), 5.91−5.85 (H-7, m, 1H), 5.78 (H-21, s, 1H), 4.82 (H-15, d, J = 1.7 Hz, 2H), 4.36 (H-17a, H-17b, H-19a, dt, J = 36.9, 12.6 Hz, 3H), 3.74−3.61 (H-19b, H-3, m, 2H), 2.61 (H-9, d, J = 10.3 Hz, 1H), 2.37−2.24 (H-29, H-6, m, 4H), 1.87 (H-2, m, 2H), 1.67 (H-1, H-5, m, 3H), 1.49 (H-18, s, 3H), 1.26 (H-30 to H-36, s, 18H), 1.03 (H-20, s, 3H), 0.88 (H-37, t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.53 (C-16), 172.08 (C-28), 143.43 (C-11), 138.87 (C-Ar), 135.32 (C-8), 132.39 (C-14), 128.95 (C-13), 128.89 (C-7), 128.34 (C-Ar), 126.97 (C-Ar), 126.21 (C-Ar), 122.56 (C-12), 95.28 (C-21), 81.42 (C-3), 69.64 (C-15), 69.51 (C-19), 66.50 (C-17), 57.80 (C-9), 49.32 (C-5), 37.15 (C-4), 36.31 (C-10), 36.07 (C-1), 34.34 (C-aliphatic ester), 33.78 (C-aliphatic ester), 31.91 (C-aliphatic ester), 29.63 (C-aliphatic ester), 29.51 (C-aliphatic ester), 29.34 (C-aliphatic ester), 29.19 (C-aliphatic ester), 29.07 (C-aliphatic ester), 25.64 (C-2), 24.99 (C-aliphatic ester), 24.73 (C-aliphatic ester), 22.69 (C-aliphatic ester), 22.35 (C-6), 21.22 (C-18), 15.90 (C-20), 14.13 (C-39). HRMS (ESI) m/z calcd for $C_{39}H_{54}O_6$ $[M + Na]^+$ 641.3818, found 641.3820.

*4.1.33. General Procedure for the Synthesis of C-17 Ester 3,19-Dihydroxy-14-deoxy-11,12-didehydroandrographolide (**9a**−**y**).* Acetonide deprotection: The deprotection of compounds **8a**−**y** at position C-3,19 with *p*-toluene sulfonic acid (PTSA) yielded compound **9a**−**y**. General calculation: To a stirred solution of **8a**−**y** (1 mmoL) in methanol (10 mL) was added *p*-Toluene sulfonic acid (PTSA) (0.5 mmoL) at room temperature for 2 h. After the stirring was continued at room temperature for 2 h, the reaction mixture was quenched with $NaHCO_3$ (aq.) (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water (10 ml), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. All the residues after deprotection reaction with PTSA were purified by column chromatography (2% methanol/dichloromethane) to afford the corresponding products (**9a**−**y**).

*4.1.34. ((1S,5i,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl Benzoate (**9a**).* Yield: 82%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (Ar-H, d, J = 7.7 Hz, 2H), 7.55 (Ar-H, t, J = 6.9 Hz, 1H), 7.44 (Ar-H, t, J = 7.5 Hz, 2H), 7.04 (H-14, s, 1H), 6.70 (H-11, dd, J = 15.6, 10.8 Hz, 1H), 6.17 (H-12, d, J = 15.8 Hz, 1H), 5.96 (H-7, s, 1H), 4.74 (H-15, s, 2H), 4.66 (H-17a, d, J = 12.4 Hz, 1H), 4.55 (H-17b, d, J = 12.5 Hz, 1H), 4.29 (H-19a, d, J = 11.0 Hz, 1H), 3.49(H-19b, H-3, t, J = 8.6 Hz, 2H), 2.65 (H-9, d, J = 9.2 Hz, 1H), 2.25 (H-6, d, J = 17.0 Hz, 2H), 2.06 (H-2, d, J = 17.2 Hz, 2H), 1.81 (H-1, H-5, dd, J = 23.8, 10.6 Hz, 3H), 1.26 (H-18, s, 3H), 0.88 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.01 (C-16), 166.11 (C-21), 143.07 (C-11), 135.50 (C-8), 132.89 (C-14), 131.87 (C-Ar), 130.37 (C-Ar), 129.52 (C-13), 129.04 (C-Ar), 128.35 (C-Ar), 127.29 (C-7), 122.36 (C-12), 81.00 (C-3), 69.56 (C-15), 67.16 (C-19), 63.98 (C-17), 58.11 (C-9), 49.92 (C-5), 38.04 (C-4), 35.88 (C-10), 29.66 (C-1), 27.74 (C-2), 23.26 (C-6), 22.22 (C-18), 15.81 (C-20). HRMS (ESI) m/z calcd for $C_{27}H_{32}O_6$ $[M + Na]^+$ 475.2097, found 475.2103.

*4.1.35. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Methoxybenzoate (**9b**).* Yield: 89%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.56 (Ar-H, m, 1H), 7.52 (Ar-H, d, J = 5.3 Hz, 1H), 7.35 (Ar-H, d, J = 7.7 Hz, 1H), 7.09 (Ar-H, H-14, dd, J = 18.1, 6.7 Hz, 2H), 6.69 (H-11, td, J = 15.6, 8.9 Hz, 1H), 6.18 (H-12, dd, J = 15.5, 7.5 Hz, 1H), 5.99−5.92 (H-7, m, 1H), 4.74 (H-15, s, 2H), 4.69−4.60 (H-17a, m, 1H), 4.60−4.49 (H-17b, m, 1H), 4.33−4.22 (H-19a, m, 1H), 3.84 (H-OCH_3, s, 3H), 3.49 (H-19b, H-3, d, J = 7.9 Hz, 2H), 2.64 (H-9, d, J = 6.2 Hz, 1H), 2.32−2.12 (H-6, m, 2H), 2.09−1.94 (H-2, m, 2H), 1.89−1.77 (H-1, H-5, m, 3H), 1.27 (H-18, s, 3H), 0.87 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.18 (C-16), 166.02 (C-21), 159.56 (C-Ar), 143.36 (C-11), 135.38 (C-8), 131.76 (C-14), 129.45 (C-13), 128.93 (C-7), 127.24 (C-Ar), 121.80 (C-12), 119.16 (C-Ar), 114.44 (C-Ar), 80.99 (C-3), 69.68 (C-15), 67.30 (C-19), 64.09 (C-17), 57.98 (C-9), 49.91 (C-5), 42.17 (C-4), 35.84 (C-10), 29.69 (C-1), 27.68 (C-2), 23.25 (C-6), 22.31 (C-18), 15.88 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{34}O_7$ $[M + Na]^+$ 505.2202, found 505.2202.

*4.1.36. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Fluorobenzoate (**9c**).* Yield: 80%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (Ar-H, d, J = 7.7 Hz, 1H), 7.71 (Ar-H, d, J = 8.8 Hz, 1H), 7.47 (Ar-H, dd, J = 13.5, 7.8 Hz, 2H), 7.13 (H-14, s, 1H), 6.76 (H-11, dd, J = 15.5, 10.6 Hz, 1H), 6.22 (H-12, d, J = 15.8 Hz, 1H), 6.00 (H-7, s, 1H), 4.81 (H-15, s, 2H), 4.71 (H-17a, d, J = 12.5 Hz, 1H), 4.60 (H-17b, d, J = 12.6 Hz, 1H), 4.34 (H-19a, d, J = 11.1 Hz, 1H), 3.54 (H-19b, H-3, dd, J = 10.9, 5.1 Hz, 2H), 2.68 (H-9, d, J = 9.0 Hz, 1H), 2.37 (H-6, dd, J = 19.7, 12.0 Hz, 2H), 2.04 (H-2, d, J = 14.5 Hz, 2H), 1.85(H-1, H-5, ddd, J = 10.7, 9.8, 4.7 Hz, 3H), 1.46 (H-18, s, 3H), 0.92 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.09 (C-16), 165.01 (C-21), (163.51, 161.54, C-Furan), 143.41 (C-11), 135.41 (C-8), 131.59 (C-14), 130.06 (C-13), 128.88 (C-7), 127.71 (C-Ar), 125.32 (C-Ar), 122.46 (C-12), 116.31 (C-Ar), 81.02 (C-3), 69.66 (C-15), 67.61 (C-19), 63.98 (C-17), 57.99 (C-9), 49.78 (C-5), 42.25 (C-4), 37.97 (C-10), 35.85 (C-1), 33.86 (C-2), 31.95 (C-6), 22.21 (C-18), 15.87 (C-20). ^{19}F NMR: δ_F -112.30 (Ar-F). HRMS (ESI) m/z calcd for $C_{27}H_{31}O_6F$ $[M + Na]^+$ 493.2002, found 493.2003.

*4.1.37. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Chlorobenzoate (**9d**).* Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (Ar-H, d, J = 14.9 Hz, 1H), 7.89 (Ar-H, d, J = 8.5 Hz, 1H), 7.52 (Ar-H,d, J = 7.9 Hz, 1H), 7.38 (Ar-H, t, J = 7.9 Hz, 1H), 7.09 (H-14, s, 1H), 6.70 (H-11, dd, J = 15.6, 10.7 Hz, 1H), 6.17 (H-12, d, J = 15.7 Hz, 1H), 5.95 (H-7, d, J = 1.7 Hz, 1H), 4.76 (H-15, s, 2H), 4.66 (H-17a, d, J = 12.5 Hz, 1H), 4.56 (H-17b, d, J = 12.6 Hz, 1H), 4.28(H-19a, d, J = 11.0 Hz,

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1H), 3.52−3.44 (H-19b, H-3, m, 2H), 2.63 (H-9, d, J = 10.1 Hz, 1H), 2.25 (H-6, d, J = 17.3 Hz, 2H), 2.08−1.93 (H-2, m, 2H), 1.88−1.78 (H-1,H-5, m, 2H), 1.25 (H-18, s, 3H), 0.87 (H-20, s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.14 (C-16), 164.94 (C-21), 143.46 (C-11), 134.46 (C-8), 132.05 (C-14), 131.58 (C-13), 129.77 (C-Ar), 128.86 (C-7), 127.84 (C-Ar), 127.63 (C-Ar), 122.20 (C-12), 80.95 (C-3), 69.68 (C-15), 67.65 (C-19), 64.09 (C-17), 57.96 (C-9), 49.87 (C-5), 42.83 (C-4), 37.99 (C-10), 29.67 (C-1), 27.67 (C-2), 23.23 (C-6), 22.31 (C-18), 15.87 (C-20). HRMS (ESI) m/z calcd for $C_{27}H_{31}O_6Cl$ $[M + Na]^+$ 509.1707, found 509.1712.

4.1.38. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Bromobenzoate ***(9e)***. Yield: 87%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (Ar-H, s, 1H), 7.98 (Ar-H, d, J = 7.8 Hz, 1H), 7.73 (Ar-H, d, J = 7.2 Hz, 1H), 7.38 (Ar-H, d, J = 7.6 Hz, 1H), 7.14 (H-14, s, 1H), 6.76 (H-11, dd, J = 15.6, 10.7 Hz, 1H), 6.22 (H-12, d, J = 15.7 Hz, 1H), 6.00 (H-7, s, 1H), 4.82 (H-15, s, 2H), 4.71 (H-17a, d, J = 12.6 Hz, 1H), 4.61 (H-17b, d, J = 12.5 Hz, 1H), 4.34 (H-19a, d, J = 11.1 Hz, 1H), 3.54 (H-19b, H-3, dd, J = 11.3, 5.5 Hz, 2H), 2.68 (H-9, d, J = 7.9 Hz, 1H), 2.42−2.26 (H-6, m, 2H), 2.07 (H-2, dd, J = 18.2, 6.2 Hz, 2H), 1.87 (H-1,H-5, dd, J = 14.8, 12.2 Hz, 3H), 1.34 (H-18, s, 3H), 0.92 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.11 (C-16), 164.82 (C-21), 143.43 (C-11), 135.91 (C-8), 135.41 (C-Ar), 132.48 (C-14), 131.58 (C-Ar), 130.08 (C-13), 128.84 (C-7), 128.21 (C-Ar), 127.78 (C-Ar), 122.48 (C-12), 81.00 (C-3), 69.69 (C-15), 67.68 (C-19), 63.99 (C-17), 57.98 (C-9), 49.74 (C-5), 42.23 (C-4), 37.95 (C-10), 35.85 (C-1), 27.71 (C-2), 23.24 (C-6), 22.21 (C-18), 15.87 (C-20). HRMS (ESI) m/z calcd for $C_{27}H_{31}O_6Br$ $[M + Na]^+$ 553.1202, found 553.1202.

4.1.39. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Iodobenzoate ***(9f)***. Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (Ar-H, s, 1H), 7.98 (Ar-H , d, J = 7.8 Hz, 1H), 7.89 (Ar-H d, J = 7.8 Hz, 1H), 7.20 (Ar-H, t, J = 7.8 Hz, 1H), 7.12 (H-14, s, 1H), 6.72 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.19 (H-12, d, J = 15.7 Hz, 1H), 5.96 (H-7, s, 1H), 4.79 (H-15, s, 2H), 4.67 (H-17a, d, J = 12.4 Hz, 1H), 4.58 (H-17b, d, J = 12.6 Hz, 1H), 4.30 (H-19a, d, J = 11.0 Hz, 1H), 3.55−3.45(H-19b, H-3, m, 2H), 2.65 (H-9, d, J = 9.3 Hz, 1H), 2.27 (H-6, d, J = 17.9 Hz, 2H), 2.04−1.85 (H-2, m, 2H), 1.82−1.70 (H-1, H-5, m, 3H), 1.27 (H-18, s, 3H), 0.89 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.48 (C-16), 166.03 (C-21), 144.84 (C-Ar), 143.15 (C-11), 139.78 (C-Ar), 136.84 (C-8), 133.68 (C-14), 133.05 (C-Ar), 131.55 (C-13), 130.17 (C-Ar), 129.19 (C-7), 123.87 (C-12), 82.30 (C-3), 71.07 (C-15), 69.04 (C-19), 65.39 (C-17), 59.43 (C-9), 51.24 (C-5), 43.61 (C-4), 39.41 (C-10), 31.08 (C-1), 29.11 (C-2), 24.69 (C-6), 23.67 (C-18), 15.49 (C-20). HRMS (ESI) m/z calcd for $C_{27}H_{31}O_6I$ $[M + Na]^+$ 601.1163, found 601.1066.

4.1.40. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl Furan-3-carboxylate ***(9g)***. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1H, d, J = 4.5 Hz, Ar-H), 7.60−7.48 (1H, m, Ar-H), 7.44 (1H, d, J = 1.3 Hz, H-14), 7.38 (1H, d, J = 7.4 Hz, Ar-H), 7.14 (1H, s, Ar-H), 6.75 (1H, dd, J = 5.8, 1.2 Hz, H-11), 6.19 (1H, d, J = 15.7 Hz, H-12), 4.80 (2H, s, H-15), 4.63 (1H, d, J = 12.1 Hz, H-19a), 4.47 (1H, d, J = 12.5 Hz, H-3), 4.31 (1H, d, J = 11.1 Hz, H-19b), 3.55−3.46 (2H, m, H-17), 2.63 (1H, d, J = 10.8 Hz, H-9), 2.46−2.25 (2H, m, H-7), 2.07 (2H, t, J = 6.5 Hz, H-2), 1.88−1.79 (2H, m, H-6), 1.76−1.72 (2H, m, H-1), 1.44 (3H, s, H-20), 0.89 (3H, s, H-18). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.94 (C-16), 165.61 (C-21), 149.15 (C-Ar), 145.13 (C-Ar), 144.57 (C-11), 136.92 (C-8), 133.18 (C-Ar), 128.85 (C-13), 123.80 (C-7), 111.19 (C-12), 82.43 (C-3), 71.00 (C-15), 67.97 (C-19), 65.38 (C-17), 59.55 C-9), 51.30 (C-5), 43.70 (C-4), 39.44 (C-10), 37.26 (C-1), 33.32 (C-2), 24.08 (C-6), 23.61 (C-18), 15.48 (C-20). HRMS (ESI) m/z calcd for $C_{25}H_{30}O_7$ $[M + Na]^+$ 465.1889, found 465.1889.

4.1.41. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-(Trifluoromethyl)benzoate ***(9h)***. Yield: 84%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.22 (Ar-H, m, 2H), 7.86 (Ar-H, d, J = 7.8 Hz, 1H), 7.64 (Ar-H, t, J = 7.7 Hz, 1H), 7.13 (H-14, s, 1H), 6.79 (H-11, dd, J = 15.6, 10.6 Hz, 1H), 6.23 (H-12, d, J = 15.7 Hz, 1H), 6.01 (H-7, s, 1H), 5.34 (H-15, s, 2H) 4.74 (H-17a, d, J = 12.3 Hz, 1H), 4.66 (H-17b, d, J = 12.4 Hz, 1H), 4.33 (H-19a, d, J = 11.1 Hz, 1H), 3.54 (H-19b, H-3, d, J = 11.6 Hz, 2H), 2.68 (H-9, d, J = 11.1 Hz, 1H), 2.44−2.16 (H-6, m, 2H), 2.07 (H-2, d, J = 12.2 Hz, 2H), 1.90−1.80 (H-1, H-5, m, 3H), 1.46 (H-18, s, 3H), 0.92 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.09 (C-16), 164.84 (C-21), 143.55 (C-11), 139.32 (C-Ar), 135.40 (C-8), 132.85 (C-14), 131.50 (C-Ar), 129.19 (C-13), 128.80 (C-7), 127.98 (C-Ar), 126.41 (C-12), 122.51 (C-12), 114.10 (C-Ar), 80.94 (C-3), 69.66 (C-15), 67.82 (C-19), 63.98 (C-17), 57.99 (C-9), 49.73 (C-5), 42.20 (C-4), 37.94 (10), 35.85 (C-1), 27.68 (C-2), 22.72 (C-6), 22.22 (18), 15.84 (C-20). ^{19}F NMR: δ_F -58.92 (Ar-3F). HRMS (ESI) m/z calcd for $C_{28}H_{31}O_6F_3$ $[M + Na]^+$543.1970, found 543.1974.

4.1.42. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Methylbenzoate ***(9i)***. Yield: 84%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (Ar-H, s, 1H), 7.86 (Ar-H, s, 1H), 7.46 (Ar-H, d, J = 7.4 Hz, 1H), 7.41 (Ar-H, d, J = 7.1 Hz, 1H), 7.10 (H-14, s, 1H), 6.75 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.22 (H-12, d, J = 15.8 Hz, 1H), 6.00 (H-7, d, J = 4.5 Hz, 1H), 4.79 (H-15, s, 2H), 4.70 (H-17a, d, J = 12.7 Hz, 1H), 4.58 (H-17b, d, J = 12.8 Hz, 1H), 4.35 (H-19a, d, J = 11.0 Hz, 1H), 3.55(H-19b, H-3, dd, J = 12.3, 7.0 Hz, 2H), 2.73−2.66 (H-9, m, 1H), 2.46 (Ar-CH_3, d, J = 3.3 Hz, 3H), 2.30 (H-6 d, J = 18.6 Hz, 2H), 2.09 (H-2, s, 2H), 1.92−1.79 (H-1,H-5, m, 3H), 1.46 (H-18, s, 3H), 0.93 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.14 (C-16), 166.36 (C-21), 143.23 (C-11), 139.32 (C-Ar), 135.47 (C-8), 134.38 (C-Ar), 133.79 (C-Ar), 130.07 (C-Ar), 128.29 (C-13), 126.68 (C-7), 122.37 (C-12), 114.10 (C-Ar), 81.05 (C-3), 69.65 (C-15), 67.10 (C-19), 64.00 (C-17), 58.02 (C-9), 49.81 (C-5), 42.23 (C-4), 37.97 (C-10), 35.84 (C-1), 33.85 (C-2), 22.72 (C-28), 22.22 (C-6), 21.33 (C-18), 15.89 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{34}O_6$ $[M + Na]^+$ 489.2253, found 489.2256.

4.1.43. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5 dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3,5-Dimethoxybenzoate ***(9j)***. Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (H-Ar, t, J = 3.3 Hz, 2H), 7.09 (H-14, d, J = 4.9 Hz, 1H), 6.68 (H-11, dd, J = 13.7, 8.6 Hz, 1H), 6.65 (H-Ar, t, J = 2.3 Hz, 1H), 6.18 (H-12, d, J = 15.7 Hz, 1H),

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5.94 (H-7, s, 1H), 4.75 (H-15, d, J = 13.2 Hz, 2H), 4.59 (H-17a, H-17b, dd, J = 35.5, 12.6 Hz, 2H), 4.27 (H-19a, dd, J = 18.6, 11.1 Hz, 1H), 3.83 (H-OCH3x2, s, 6H), 3.52−3.46 (H-19b, H-3, m, 2H), 2.64 (H-9, d, J = 9.8 Hz, 1H), 2.32−2.05 (H-6, m, 2H), 1.97 (H-2,m, 2H), 1.77−1.66 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.87 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.30 (C-16), 165.93 (C-21), 160.63 (C-Ar), 143.48 (C-11), 135.39 (C-8), 132.15 (C-14), 131.68 (C-13), 128.87 (C-7), 127.30 (C-Ar), 122.38 (C-12), 107.28 (C-Ar), 105.27 (C-Ar), 80.92 (C-3), 69.75 (C-15), 67.41 (C-19), 64.01 (C-17), 57.92 (C-9), 55.63 (C-OCH3x2), 49.74 (C-5), 42.11 (C-4) 37.94 (C-10), 35.81 (C-1), 27.60 (C-2), 23.20 (C-6), 22.24 (C-18), 15.86 (C-20). HRMS (ESI) m/z calcd for $C_{29}H_{36}O_8$ $[M + Na]^+$ 535.2308, found 535.2308.

*4.1.44. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3,4,5-Trimethoxybenzoate (**9k**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (H-Ar, s, 2H), 7.11 (H-14, s, 1H), 6.71 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.19 (H-12, d, J = 15.7 Hz, 1H), 5.93 (H-7, s, 1H), 4.77 (H-15, s, 2H), 4.60 (H-17a, H-17b, dd, J = 33.4, 12.8 Hz, 2H), 4.29 (H-19a, d, J = 11.1 Hz, 1H), 3.91 (H-OCH3x2, s, 6H), 3.91 (H-OCH3, s, 3H), 3.53−3.44 (H-19b, H-3, m, 2H), 2.63 (H-9, d, J = 10.8 Hz, 1H), 2.18 (H-6, m, 2H), 1.88 (H-2, m, 2H), 1.77−1.68 (H-1, H-6, m, 3H), 1.25 (H-18, s, 3H), 0.88 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.23 (C-16), 165.84 (C-21), 152.92 (C-Ar), 143.39 (C-11), 135.46 (C-8), 131.70 (C-14), 128.87 (C-13), 126.87 (C-7), 125.27 (C-Ar), 122.34 (C-12), 106.80 (C-Ar), 80.89 (C-3), 69.74 (C-15), 67.10 (C-19), 63.99 (C-17), 60.96 (C-OCH3x2-Ar), 58.05 (C-OCH3-Ar), 56.31 (C-9), 49.77 (C-5), 42.11 (C-4), 37.94 (C-10), 35.84 (C-1), 27.59 (C-2), 23.20 (C-6), 22.24 (C-18), 15.82 (C-20). HRMS (ESI) m/z calcd for $C_{30}H_{38}O_9$ $[M + Na]^+$ 565.2414, found 565.2413.

*4.1.45. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 3-Chloro-4-methoxybenzoate (**9l**).* Yield: 89%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (H-Ar, d, J = 2.1 Hz, 1H), 7.92 (H-Ar, dd, J = 8.6, 2.1 Hz, 1H), 7.12 (H-14, s, 1H), 6.99−6.94 (H-Ar, m, 1H), 6.71 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.18 (H-12, d, J = 15.7 Hz, 1H), 5.94 (H-7, d, J = 4.7 Hz, 1H), 4.78 (H-15, s, 2H), 4.64 (H-17a, d, J = 12.7 Hz, 1H), 4.53 (H-17b, d, J = 12.5 Hz, 1H), 4.28 (H-19a, t, J = 8.9 Hz, 1H), 3.97 (H-OCH3, s, 3H), 3.53−3.44 (H-19b , H-3, m, 2H), 2.63 (H-9, d, J = 9.9 Hz, 1H), 2.25 (H-6, m, 2H), 1.95 (H-2, m, 2H), 1.79−1.68 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.87 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.25 (C-16), 164.96 (C-21), 158.64 (C-Ar), 143.53 (C-11), 135.44 (C-8), 131.73 (C-14), 131.49 (C-Ar), 129.97 (C-13), 128.85 (C-7), 127.51 (C-Ar), 123.40 (C-Ar), 122.38 (C-12), 111.32 (C-Ar), 80.92 (C-3), 69.73 (C-15), 67.32 (C-19), 64.01 (C-17), 58.00 (C-OCH3-Ar), 56.39 (C-9), 49.75 (C-5), 42.12 (C-4), 37.95 (C-10), 35.83 (C-1), 27.63 (C-2), 23.22 (C-6), 22.24 (C-18), 15.86 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{33}O_7Cl$ $[M + Na]^+$ 539.1813, found 539.1813.

*4.1.46. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 4-Bromo-2-fluorobenzoate (**9m**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (H-Ar, dd, J = 6.3, 2.6 Hz, 1H), 7.64−7.60 (H-Ar, m, 1H), 7.16 (H-14, s, 1H), 7.05 (H-Ar, t, J = 9.5 Hz, 1H), 6.69 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.20 (H-12, d, J = 15.7 Hz, 1H), 5.98 (H-7, s, 1H), 4.80 (H-15, s, 2H), 4.62 (H-17a, H-17b, dd, J = 26.2, 12.5 Hz, 2H), 4.30 (H-19a, d, J = 11.1 Hz, 1H), 3.53−3.46 (H-19b, H-3, m, 2H), 2.64 (H-9, d, J = 10.0 Hz, 1H), 2.42−2.19 (H-6, m, 2H), 2.05−1.89 (H-2, m, 2H), 1.81−1.71 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.86 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.24 (C-16), 162.74 (C-21), 159.61 (C-Ar), 143.59 (C-11), 137.29 (C-Ar), 137.20 (C-Ar), 135.27 (C-8), 134.67 (C-Ar), 131.32 (C-14), 128.87 (C-13), 128.12 (C-7), 122.58 (C-12), 119.06 (C-Ar), 118.82 (C-Ar), 116.47 (C-Ar), 80.92 (C-3), 69.75 (C-15), 68.10 (C-19), 64.01 (C-17), 57.79 (C-9), 49.70 (C-5), 42.10 (C-4), 37.93 (C-10), 35.79 (C-1), 27.60 (C-2), 23.25 (C-6), 22.22 (C-18), 15.83 (C-20). ^{19}F NMR: δ_F -111.17 (Ar-F). HRMS (ESI) m/z calcd for $C_{27}H_{30}BrFO_6$ $[M + Na]^+$ 571.1107, found 571.1119.

*4.1.47. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(Trifluoromethyl)benzoate (**9n**).* Yield: 80%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.72 (H-Ar, m, 2H), 7.62 (H-Ar, dd, J = 6.1, 3.0 Hz, 2H), 7.16 (H-14, s, 1H), 6.67 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.19 (H-12, d, J = 15.8 Hz, 1H), 6.00−5.97 (H-7, m, 1H), 4.80 (H-15, s, 2H), 4.66 (H-17a, d, J = 12.2 Hz, 1H), 4.55 (H-17b, d, J = 12.4 Hz, 1H), 4.28 (H-19a, d, J = 11.1 Hz, 1H), 3.51−3.44 (H-19b, H-3, m, 2H), 2.63 (H-9, d, J = 10.1 Hz, 1H), 2.38−2.05 (H-6, m, 2H), 1.87 (H-2, m, 2H), 1.70 (H-2, H-5, m, 3H), 1.24 (H-18, s, 3H), 0.86 (H-20, s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.32 (C-16), 166.37 (C-21), 143.57 (C-11), 135.28 (C-8), 131.84 (C-14), 131.18 (C-13), 130.24, 128.87 (C-7), 128.71 (C-Ar), 126.71 (C-Ar), 126.66 (C-CF3), 122.58 (C-12), 80.89 (C-3), 69.76 (C-15), 68.42 (C-19), 64.03 (C-17), 57.74 (C-9), 49.71 (C-5), 42.08 (C-4), 37.97 (C-10), 35.80 (C-1), 27.61 (C-2), 23.26 (C-6), 22.27 (C-18), 15.83 (C-20). ^{19}F NMR: δ_F -59.25 (Ar-3F). HRMS (ESI) m/z calcd for $C_{28}H_{31}F_3O_6$ $[M + Na]^+$ 543.1970, found 543.1976.

*4.1.48. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-Phenylacetate (**9o**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (Ar-H, dd, J = 16.1, 6.4 Hz, 5H), 6.98 (H-14, s, 1H), 6.53 (H-11, dd, J = 15.7, 10.7 Hz 1H), 5.93 (H-12, d, J = 15.7 Hz, 1H), 5.78 (H-7, s, 1H), 4.72 (H-15, s, 2H), 4.38 (H-17a, d, J = 12.3 Hz, 1H), 4.28−4.19 (H-17b, H-19a, m, 2H), 3.55 (CH_2-Phenyl, s, 2H), 3.45−3.37 (H-19b, H-3, m, 2H), 2.43 (H-9, d, J = 10.2 Hz, 1H), 2.20−1.95 (H-6, m, 2H), 1.93−1.77 (H-2, m, 2H), 1.76−1.63 (H-1, H-5, m, 3H), 1.22 (H-18, s, 3H), 0.76 (H-20, s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.35 (C-16), 171.22 (C-21), 143.55 (C-11), 135.29 (C-8), 134.16 (C-Ar), 131.62 (C-14), 129.40 (C-13), 128.84 (C-Ar), 128.53 (C-7), 127.92 (C-Ar), 127.08 (C-Ar), 122.32 (C-12), 80.87 (C-3), 69.75 (C-15), 67.30 (C-19), 64.02 (C-17), 57.70 (C-9), 49.73 (C-5), 42.08 (C-4), 41.48 (C-21-CH2-phenyl), 37.96 (C-10), 35.70 (C-1), 29.72 (C-2), 23.19 (C-6), 22.29 (C-18), 15.80 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{34}O_6$ $[M + Na]^+$ 489.2253, found 489.2259.

*4.1.49. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(4-Fluorophenyl)acetate (**9p**).* Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (H-Ar, m, 2H), 7.09 (H-14, t, J = 1.9 Hz, 1H), 7.02−6.97 (H-Ar, m, 2H), 6.61 (H-

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11, dd, J = 15.7, 10.6 Hz, 1H), 6.02 (H-12, d, J = 15.7 Hz, 1H), 5.85−5.80 (H-7, m, 1H), 4.79 (H-15, d, J = 1.8 Hz, 2H), 4.41 (H-17a, d, J = 12.3 Hz, 1H), 4.28 (H-17b, H-19a, dd, J = 14.3, 11.9 Hz, 2H), 3.57 (H-22, s, 2H), 3.49−3.43 (H-19b, H-3, m, 2H), 2.48 (H-9, d, J = 10.4 Hz, 1H), 2.25−1.99 (H-6, m, 2H), 1.92−1.78 (H-2, m, 2H), 1.71−1.41 (H-1, H-5, m, 3H), 1.24 (H-18, s, 3H), 0.81 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.26 (C-16), 171.11 (C-21), 163.17 (C-Ar), 160.73 (C-Ar), 143.50 (C-11), 135.36 (C-8), 131.55 (C-14), 130.99 (C-13), 130.91 (C-Ar), 129.85 (C-7), 128.83 (C-Ar) , 128.04 (C-Ar), 122.30 (C-12), 115.43 (C-Ar), 115.22 (C-Ar), 80.89 (C-3), 69.71 (C-15), 67.33 (C-19), 63.98 (C-17), 57.87 (C-9), 49.76 (C-5), 42.12 (C-4), 40.50 (C-CH2-Phenyl), 37.96 (C-10), 35.74 (C-1), 27.63 (C-2), 23.21 (C-6), 22.26 (C-18), 15.75 (C-20). ^{19}F NMR: δ_F -115.72 (Ar-F). HRMS (ESI) m/z calcd for $C_{28}H_{33}O_6F$ $[M + Na]^+$ 507.2159, found 507.2158.

*4.1.50. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(4-Chlorophenyl)acetate (**9q**).* Yield: 85%. White solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.40−7.35 (H-Ar, m, 1H), 7.28 (H-Ar, dd, J = 5.1, 4.1 Hz, 1H), 7.23 (H-Ar, dt, J = 4.1, 2.6 Hz, 2H), 7.13 (H-14, s, 1H), 6.59 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.03 (H-12, d, J = 15.6 Hz, 1H), 5.84 (H-7, s, 1H), 4.79 (H-15, s, 2H), 4.38 (H-17a, H-17b, dd, J = 31.6, 12.3 Hz, 2H), 4.24 (H-19a, dd, J = 14.5, 8.3 Hz, 1H), 3.73 (H-22, s, 2H), 3.49−3.41 (H-19b, H-3, m, 2H), 2.49 (H-9, d, J = 10.2 Hz, 1H), 2.24−1.97 (H-6, m, 2H), 1.87−1.74 (H-2, m, 2H), 1.67−1.44 (H-1, H-5, m, 3H), 1.24 (H-18, s, 3H), 0.81 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.39 (C-16), 170.24 (C-21), 143.58 (C-11), 135.34 (C-8), 134.49 (C-Ar), 132.51 (C-14), 131.69 (C-13), 131.55 (C-7), 129.42, 128.90 (C-Ar), 128.71(C-Ar), 127.98 (C-Ar), 126.94(C-Ar), 122.35 (C-12), 80.84 (C-3), 69.78 (C-15), 67.45 (C-19), 64.02 (C-17), 57.72 (C-9), 49.73 (C-5), 42.04 (C-4), 39.20 (C-CH2-Phenyl), 37.98 (C-10), 35.71 (C-1), 27.59 (C-2), 23.19 (C-6), 22.30 (C-18), 15.80 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{33}O_6Cl$ $[M + Na]^+$ 523.1863, found 523.1862.

*4.1.51. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(4-Iodophenyl)acetate (**9r**).* Yield: 85%. White solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.63 (H-Ar, d, J = 8.3 Hz, 2H), 7.07 (H-14, d, J = 2.1 Hz, 1H), 7.01 (H-Ar, t, J = 5.3 Hz, 2H), 6.64−6.56 (H-11, m, 1H), 6.01 (H-12, d, J = 15.7 Hz, 1H), 5.85−5.81 (H-7, m, 1H), 4.79 (H-15,d, J = 1.6 Hz, 2H), 4.39 (H-17a, d, J = 12.3 Hz, 1H), 4.34−4.21 (H-17b, H-19a, m, 2H), 3.53 (H-22, s, 2H), 3.47 (H-19b, H-3, d, J = 10.5 Hz, 2H), 2.46 (H-9, d, J = 10.3 Hz, 1H), 2.23−1.97 (H-6, m, 2H), 1.91−1.75 (H-2, m, 2H), 1.59 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.80 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.24 (C-16), 170.66 (C-21), 143.57 (C-11), 137.55 (C-Ar), 135.33 (C-8), 133.83 (C-Ar), 131.53 (C-14)), 131.47 (C-13), 128.80 (C-7), 128.32 (C-Ar), 122.33 (C-12), 80.92 (C-3), 69.74 (C-15), 67.48 (C-19), 63.98 (C-17), 57.83 (C-9), 49.76 (C-5), 42.15 (C-4), 40.90 (C-CH2-Phenyl), 37.96 (C-10), 35.73 (C-1), 27.65 (C-2), 23.22 (C-6), 22.27 (C-18), 15.76 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{33}O_6I$ $[M + Na]^+$ 615.1220, found 615.1215.

*4.1.52. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(4-Methoxyphenyl)acetate (**9s**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.16 (H-Ar, m, 2H), 7.04 (H-14, s, 1H), 6.87−6.83 (H-Ar, m, 2H), 6.57 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.00 (H-12, d, J = 15.7 Hz, 1H), 5.82 (H-7, d, J = 2.7 Hz, 1H), 4.77 (H-15, d, J = 1.6 Hz, 2H), 4.41 (H-17a, d, J = 12.3 Hz, 1H), 4.30−4.20 (H-17b, H-19b, m, 2H), 3.79 (H-OCH_3, s, 3H), 3.56 (H-22, s, 2H), 3.47 (H-19a, H-3, d, J = 10.1 Hz, 2H), 2.48 (H-9, d, J = 9.6 Hz, 1H), 2.28−2.04 (H-6, m, 2H), 1.97−1.82 (H-2, m, 2H), 1.73−1.60 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.81 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.26 (C-16), 171.52 (C-21), 158.64 (C-Ar), 143.40 (C-11), 135.31 (C-8), 131.67 (C-14), 130.93 (C-13), 130.39 (C-Ar), 130.32(C-Ar), 128.91 (C-7), 128.82 (C-Ar), 127.79 (C-Ar), 126.23 (C-Ar), 122.32 (C-12), 113.92 (C-Ar), 80.96 (C-3), 69.70 (C-15), 67.19 (C-19), 63.99 (C-17), 57.73 (C-9), 55.31 (C-OCH3), 49.76 (C-5), 42.17 (C-4), 40.54 (C-CH2-Phenyl), 37.96 (C-10), 35.72 (C-1), 27.67 (C-2), 23.73 (C-6), 22.24 (C-18), 15.78 (C-20), 14.08, 10.98. HRMS (ESI) m/z calcd for $C_{29}H_{36}O_7$ $[M + Na]^+$ 519.2359, found 519.2363.

*4.1.53. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(p-Tolyl)acetate (**9t**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (H-Ar, m, 4H), 7.03 (H-14, t, J = 1.9 Hz, 1H), 6.56 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 5.99 (H-12, d, J = 15.7 Hz, 1H), 5.84−5.79 (H-7, m, 1H), 4.77 (H-15, d, J = 1.7 Hz, 2H), 4.41 (H-17a, d, J = 12.4 Hz, 1H), 4.27 (H-17b, H-19b, dd, J = 11.7, 6.5 Hz, 2H), 3.55 (H-22, s, 2H), 3.47−3.44 (H-19a, H-3, m, 2H), 2.47 (H-9, d, J = 9.0 Hz, 1H), 2.33 (H-Ar-CH3, s, 3H), 2.23−2.00 (H-6, m, 2H), 1.92 (H-2, m, 2H), 1.74−1.59 (H-1, H-5, m, 3H), 1.24 (H-18, s, 3H), 0.80 (H-20 s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.35 (C-16), 171.45 (C-21), 143.48 (C-11), 136.64 (C-Ar), 135.30 (C-8), 131.64 (C-14), 131.06 (C-13), 129.24 (C-7), 129.20 (C-Ar), 127.78 (C-Ar), 122.31 (C-12), 80.87 (C-3), 69.74 (C-15), 67.20 (C-19), 64.01 (C-17), 57.70 (C-9), 49.73 (C-5), 42.06 (C-4), 41.02 (C-CH2-Phenyl), 37.95 (C-10), 35.70 (C-1), 27.61 (C-2), 23.18 (C-6), 22.29 (C-29-Ar), 21.11 (C-18), 15.79 (C-20). HRMS (ESI) m/z calcd for $C_{29}H_{36}O_6$ $[M + Na]^+$ 503.2410, found 503.2413.

*4.1.54. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(3,4,5-Trimethoxyphenyl)acetate (**9u**).* Yield: 90%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (H-14, s, 1H), 6.61 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.50 (H-Ar, s, 2H), 5.91 (H-12, d, J = 15.7 Hz, 1H), 5.87−5.83 (H-7, m, 1H), 4.78 (H-15, s, 2H), 4.41 (H-17a, d, J = 12.3 Hz, 1H), 4.28 (H-17b, H-19a, dd, J = 17.3, 11.7 Hz, 2H), 3.85 (H-OCH3x2, s, 6H), 3.82 (H-OCH3, s, 3H), 3.53 (H-22, s, 2H), 3.49−3.42 (H-19b, H-3, m, 2H), 2.47 (H-9, d, J = 10.6 Hz, 1H), 2.26−1.96(H-6, m, 2H), 1.88−1.74 (H-2, m, 2H), 1.68−1.35 (H-1, H-5, m, 3H), 1.24 (H-18, s, 3H), 0.81 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.27 (C-16), 171.11 (C-21), 153.12 (C-Ar), 143.88 (C-11), 136.86 (C-Ar), 135.09 (C-8), 131.70 (C-14), 129.86 (C-13), 128.60 (C-7), 128.03 (C-Ar), 122.39 (C-12), 106.39 (C-Ar), 80.90 (C-3), 69.76 (C-15), 67.44 (C-19), 63.97 (C-17), 60.86 (C-OCH3), 57.87 (C-9), 56.12 (C-OCH3), 49.83 (C-5), 42.09 (C-4), 41.67 (C-CH2-Phenyl), 37.99 (C-10), 35.72 (C-1), 27.61 (C-2), 23.21 (C-6), 22.28 (C-18), 15.76 (C-20). HRMS (ESI) m/z calcd for $C_{31}H_{40}O_9$ $[M + Na]^+$ 579.2570, found 579.2571.

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*4.1.55. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl 2-(3,4-Dichlorophenyl)acetate (**9v**).* Yield: 85%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.39 (H-Ar, m, 1H), 7.38−7.34 (H-Ar, m, 2H), 7.11 (H-14, t, J = 2.3 Hz, 1H), 6.63 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.01 (H-12, d, J = 15.7 Hz, 1H), 5.87−5.83 (H-7, m, 1H), 4.80 (H-15, d, J = 1.7 Hz, 2H), 4.43−4.24 (H-17a, H-17b, H-19a, m, 3H), 3.56 (H-22, s, 2H), 3.47 (H-19b, H-3, m, 2H), 2.46 (H-9, d, J = 10.4 Hz, 1H), 2.16(H-6, m, 2H), 2.01−1.81 (H-2, m, 2H), 1.77−1.62 (H-1, H-5, m, 3H), 1.25 (H-18, s, 3H), 0.81 (H-20, s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.26 (C-16), 170.23 (C-21), 143.71 (C-11), 135.36 (C-8), 134.31 (C-Ar), 132.33 (C-14), 131.46−131.37 (C-Ar), 131.20 (C-13), 130.39 (C-7), 129.00−128.75 (C-Ar), 128.73 (C-Ar), 122.31 (C-12), 80.87 (C-3), 69.75 (C-15), 67.70 (19), 63.97 (C-17), 57.89 (C-9), 49.74 (C-5), 42.11 (C-4), 40.39 (C-CH2-Phenyl), 37.93 (C-10), 35.74 (C-1), 27.62 (C-2), 23.25 (C-6), 22.25 (C-18), 15.73 (C-20). HRMS (ESI) m/z calcd for $C_{28}H_{32}O_6Cl_2$ $[M + Na]^+$ 557.1474, found 55.1479.

*4.1.56. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl Octanoate (**9w**).* Yield: 85%. White liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (H-14, s, 1H), 6.64 (H-11, dd, J = 15.7, 10.6 Hz, 1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.85 (H-7, d, J = 2.2 Hz, 1H), 4.83 (H-15, d, J = 7.2 Hz, 2H), 4.39 (H-17a, d, J = 13.0 Hz, 1H), 4.28 (H-17b,H-19a, dd, J = 11.9, 2.9 Hz, 2H), 3.52−3.42 (H-19b, H-3 m, 2H), 2.57 (H-9, d, J = 10.4 Hz, 1H), 2.34−2.20 (H-6, H-22, m, 4H), 1.96 (H-2, m, 2H), 1.72 (H-1, H-5, m, 3H), 1.29−1.25 (H-18, H-33 to H-27, m, 13H), 0.87 (H-20, H-28, m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.59 (C-16), 172.23 (C-21), 143.33 (H-11), 135.54 (H-8), 131.80 (C-14), 128.97 (C-13), 127.04 (C-7), 122.24 (C-12), 80.90 (C-3), 69.71 (C-15), 66.50 (C-19), 64.01 (C-17), 57.92 (C-9), 49.79 (C-5), 42.11 (C-4), 37.98 (C-10), 35.78 (C-aliphatic ester), 34.32 (C-aliphatic ester), 31.67 (C-aliphatic ester), 29.10 (C-1), 28.94 (C-aliphatic ester), 27.63 (C-2), 24.96 (C-aliphatic ester), 23.16 (C-aliphatic ester), 22.59 (C-6), 22.26 (C-18), 15.81 (C-20), 14.08 (C-28-(C-aliphatic ester). HRMS (ESI) m/z calcd for $C_{28}H_{42}O_6$ $[M + Na]^+$ 497.2879, found 497.2879.

*4.1.57. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl Decanoate (**9x**).* Yield: 87%. White liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (H-14, d, J = 1.8 Hz, 1H), 6.64 (H-11, dd, J = 15.7, 10.7 Hz, 1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.86 (H-7, s, 1H), 4.81 (H-15, s, 2H), 4.39 (17a, d, J = 12.5 Hz, 1H), 4.32−4.25 (H-17b, H-19a, m, 2H), 3.47 (H-19b, H-3, m, 2H), 2.57 (H-9, d, J = 10.3 Hz, 1H), 2.28 (H-6, H-22, m, 4H), 2.00−1.85 (H-2, m, 2H), 1.76−1.66 (H-1, H-5, m, 3H), 1.25 (H-18, H-23 to H-29, m, 17H), 0.85 (H-20, H-30, m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.55 (C-16), 172.17 (C-21), 143.24 (C-11), 135.55 (C-8), 131.83 (C-14), 129.01 (C-13), 126.99 (C-7), 122.25 (C-12), 80.95 (H-3), 69.67 (C-15), 66.47 (C-19), 64.00 (C-17), 57.94 (C-9), 49.82 (C-5), 42.15 (C-4), 37.99 (C-10), 35.79 (C-aliphatic esters), 34.32 (C-aliphatic esters), 31.85 (C-aliphatic ester), 29.43 (C-1) , 29.28 (C-aliphatic esters), 29.25 (C-aliphatic esters), 29.15 (C-aliphatic esters), 27.65 (C-2), 24.96 (C-aliphatic esters), 23.17 (C-aliphatic esters), 22.64 (C-6), 22.24 (C-18), 15.80 (C-20), 14.09 (C-30-aliphatic ester). HRMS (ESI) m/z calcd for $C_{30}H_{46}O_6$ $[M + Na]^+$ 525.3192, found 525.3193.

*4.1.58. ((1S,5R,6R,8aR)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-1-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)vinyl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)methyl Dodecanoate (**9y**).* Yield: 87%. White liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (H-14, s, 1H), 6.63 (H-11, dd, J = 15.6, 10.7 Hz, 1H), 6.16 (H-12, d, J = 15.7 Hz, 1H), 5.84 (H-7, s, 1H), 4.81 (H-15, s, 2H), 4.39 (H-17a, d, J = 12.6 Hz, 1H), 4.30−4.22 (H-17b, H-19a, m, 2H), 3.46 (H-19b, H-3, m, 2H), 2.56 (H-9, d, J = 10.3 Hz, 1H), 2.32−2.18 (H-6, H-22, m, 4H), 2.00−1.81 (H-2, m, 2H), 1.76−1.65 (H-1, H-5, m, 3H), 1.25 (H-18, H-23 to H-31, m, 21H), 0.86 (H-20, H-32, m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.63 (C-16), 172.27 (C-21), 143.39 (C-11), 135.53 (C-8), 131.78 (C-14), 128.94 (C-13), 127.02 (C-7), 122.24 (C-12), 80.88 (H-3), 69.74 (C-15), 66.52 (C-19), 64.01 (C-17), 57.91 (C-9), 49.77 (C-5), 42.07 (C-4), 37.97 (C-10), 35.77 (C-aliphatic esters), 34.32 (C-aliphatic esters), 31.90 (C-aliphatic ester), 29.70 (C-1), 29.61 (C-aliphatic ester), 29.50 (C-aliphatic ester), 29.33 (C-aliphatic ester), 29.31 (C-aliphatic ester), 29.17 (C-aliphatic ester), 27.60 (C-2), 24.97 (C-aliphatic esters), 23.16 (C-aliphatic ester), 22.69 (C-6), 22.28 (C-18), 15.83 (C-20), 14.14 (C-32-aliphatic ester). HRMS (ESI) m/z calcd for $C_{32}H_{50}O_6$ $[M + Na]^+$ 553.3505, found 553.3510.

4.2. Biology. *4.2.1. Cell Culture and Growth Conditions.* A panel of human cancer cell lines procured from the European Collection of Authenticated Cell Cultures (ECACC) was used for this study, which included lung cancer A549, prostate cancer PC-3, colon cancer HCT-116, and breast cancer MCF-7. Cell lines A549, PC-3, and HCT-116 were cultured using RPMI media, and MCF-7 was cultured using DMEM, supplemented with 10% FBS, 100 U penicillin, 100 U streptomycin, 0.5 mM sodium pyruvate, and 10 mM HEPES in a humidified atmosphere at 37 °C, 5% CO_2, and 95% humidity in an incubator.

4.2.2. MTT Assay for Cytotoxicity Assay in A549 Cells. In general, the viability of cells was estimated by an MTT assay, a calorimetric technique. This assay identifies the reduction of MTT [3-(4,5-dimethylthiazolyl)-2,5-diphenyl-tetrazolium bromide] (Sigma) by mitochondrial dehydrogenase to purple formazan product, which reflects the normal function of mitochondria and hence the measurement of cytotoxicity cell and viability. Briefly, cell densities of 1×10^6 viable cells/well for A549, 1×10^9 viable cells/well for HCT-116, 7×10^6 viable cells/well for MCF-7, and 8×10^4 viable cells/well for PC-3 were seeded in 96-well flat-bottom plates in complete culture media (CCM). After 24 h of incubation under culture conditions, the cells were exposed to RS molecules in a complete growth medium. The plates were kept under incubation under similar conditions for 48 h at 37 °C. Further, the cells were incubated with MTT (250 μg/mL in Dulbecco's PBS) at 37 °C for 4 h. DMSO was used to dissolve the formazan produced. The resulting colored solution was quantified by estimating absorbance at 570 nm using a microplate reader (Bio-Rad Plate Reader), and IC_{50} was determined by using GraphPad Prism Software Version 5.0. Experiments were executed in triplicate, and results were expressed as mean ± SE. The percentage cell viability of cells was calculated using the following formula:

$$\text{Cell viability} = OD_{(\text{treated})}/OD_{(\text{control})} \times 100$$

The percentage cell cytotoxicity was calculated as:

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$$\text{Cytotoxicity} = 100 - [\text{OD}_{(\text{treated})}/\text{OD}_{(\text{control})} \times 100]$$

where $\text{OD}_{\text{control}}$ is the optical density for untreated cells and $\text{OD}_{\text{treated}}$ is the optical density for cells treated with compounds.

4.2.3. DAPI Staining for Analyzing Induction of Apoptosis. A549 cells (3×10^4) were seeded in 2 mL of complete growth media in each well of six-well plates for 48 h at 37 °C and 5% CO_2 in humidified air in an incubator. The cells were treated with three different concentrations of **9s** for 48 h. After treatment, media containing molecule were removed, and cells were washed with PBS and fixed in ice-cold 4% paraformaldehyde for 20 min. Subsequently, cells were permeabilized with 0.25% Triton-X-100 and stained with fluorescent nuclear dye DAPI at a final concentration of 1 μg/mL. After 30 min of incubation, cells were washed with PBS and observed for fluorescence intensity.

4.2.4. ROS Activity for Analysis of Intracellular ROS Using DCFHDA Staining. The A549 (3×10^4) cells were seeded in 2 mL of complete growth media in each well of six-well plates and allowed to adhere for another 24 h at 37 °C in a humidified CO_2 incubator. The cells were than treated with three different concentrations of **9s** molecule for 48 h. After treatment, cells were incubated with 10 μM DCFHDA dye (Sigma Aldrich) for 30 min at 37 °C. H_2O_2 (0.05%) was used as a positive control that is known to increase intracellular ROS generation. The medium was then replaced with PBS in each well. Fluorescence images were captured using fluorescence microscopy and were used to analyze ROS generation in A549 cells.

4.2.5. Measurement of Mitochondrial Membrane Potential (MMP) (ΛΨm). Mitochondrial membrane potential (MMP) in A549 cells was measured using rhodamine-123 staining, which preferentially enters into active mitochondria on the basis of its negative potential MMP. Briefly, A549 (3×10^4) cells were seeded in 2 mL of complete growth media in each well of six-well plates and allowed to adhere for 24 h at 37 °C in a unified CO_2 incubator. The cells were than treated with three different concentrations of compound **9s** for 48 h. After treatment, cells were incubated with 10 μM Rh-123 dye (Sigma Aldrich) for 30 min at 37 °C, washed with PBS, and analyzed using fluorescence microscopy. The depolarization caused by MMP led to the loss of rhodamine-123 from the mitochondria, which was accompanied by a reduction in fluorescence.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00036.

^{1}H NMR, ^{13}C NMR, and HRMS spectra for compounds **1**−**7**, **8a**−**8y**, and **9a**−**9y** and crystallographic data (single crystal X-ray diffractometer) of compounds **4** and **5** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Ravi Shankar − *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0001-9428-0354; Email: rshankar@iiim.ac.in, rshankar@iiim.res.in

Shashank K. Singh − *Pharmacology Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*; Email: sksingh @iiim.res.in

Authors

Gulshan Kumar − *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Sonia Thapa − *Pharmacology Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Javeed Ahmad Tali − *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Davinder Singh − *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-4712-7493

Bhupesh Kumar Sharma − *Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Kamakshya Nath Panda − *Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand 247667, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c00036

Notes

The authors declare no competing financial interest.

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