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Synthesis of some monocyclic analogues of mycophenolic acid via the Johnson ortho ester Claisen rearrangement

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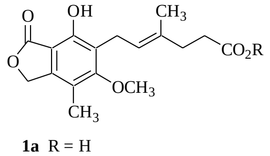
Abstract—The synthesis of some monocyclic analogues of mycophenolic acid in which the lactone ring has been eliminated, leaving the aromatic ring intact and the same oxygenated substituents flanking the hexenoic acid side chain with an (*E*)-geometry at the double bond, has been accomplished via the Johnson ortho ester Claisen rearrangement. The synthetic methodology reported here allows the preparation of mycophenolic acid analogues bearing alkyl substituents at the α- and β-positions on the side chain.

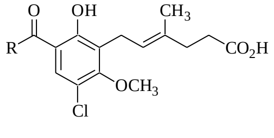
1. Introduction

In the more than 100 years since its discovery,[1] mycophenolic acid (MPA) **1a** has been the subject of intensive in vivo and in vitro biological evaluations including antifungal,[2] antibacterial,[3] and immunosuppressive properties.[4] MPA is an inhibitor of inosine-5′-monophosphate dehydrogenase[5] (IMPDH), a key enzyme in the de novo biosynthesis of guanine nucleotides causing a suppression of lymphocyte activity in humans;[6] this inhibition is believed to mediate its immunosuppresive activity. Mycophenolate mofetil **1b** (MMF), the morpholinoethyl ester prodrug of MPA has been found to be clinically effective for the reversal and prevention of kidney and heart transplant rejection; **1b** was approved in the United States in 1995 for use in renal transplant patients[7] and in 1998 for heart transplant procedures.[8]

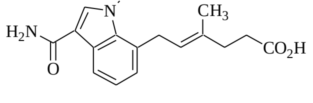
MPA itself has been tested clinically against various tumors without success. The major drawback with MPA as an anticancer drug in humans is its conjugation with glucoronic acid, a process that makes it extremely difficult to achieve the drug levels needed for anticancer activity.[9] The MPA structure has been extensively modifieds,[10] and, except for those kinds of derivatives that can be transformed to MPA in vivo, the reported compounds are inactive or have a diminished activity. In 1996, Anderson et al.[11] obtained the first monocyclic analogues, **2**, of MPA with anticancer activity although with 2 orders of magnitude less potency than MPA. Three novel indole analogues were also reported by Lai and Anderson[12] in which the carboxamide derivative **3** was selected for advanced studies against prostate cancer.



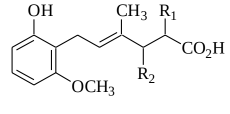
1a R = H
1b R = ethylmorpholine



2a R = CH$_3$
2b R = CH$_3$O



3



4a R$_1$ = R$_2$ = H
4b R$_1$ = CH$_3$, R$_2$ = H
4c R$_1$ = C$_2$H$_5$, R$_2$ = H
4d R$_1$ = H, R$_2$ = CH$_3$
4e R$_1$ = CH$_3$, R$_2$ = CH$_3$

Keywords: Mycophenolic acid; Ortho esters; Claisen–Johnson rearrangement.

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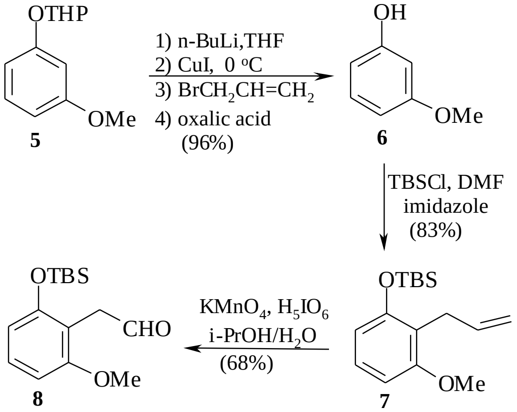
2. Results and discussion

In this paper, we report the synthesis of the monocyclic analogues **4** of MPA, these compounds have been designed as potential anticancer drugs, maintaining some structural features essential for biological activity in MPA. Although the lactone ring has been eliminated, the hexenoic acid side chain with an (*E*)-geometry at the double bond remains unchanged. Furthermore, the phenolic and methoxy functionalities in the aromatic ring surrounding the side chain also remain unchanged, particularly the free phenolic function, which is an absolute requirement for MPA activity.[13]

A prominent structural feature of analogues **4** is the presence of an (*E*)-trisubstituted double bond, which along with its γ,δ relationship to the carboxylic carbonyl group satisfy the structural prerequisite for the Johnson ortho ester Claisen rearrangement,[14] the most powerful method for the synthesis of γ,δ-unsaturated carbonyl compounds.[15]

The allyl alcohols **9a** and **9b** needed for the Claisen process were prepared from aldehyde **8**, which, in turn, was obtained from the protected phenol **5** (Scheme 1). The THP protected 3-methoxyphenol **5** was functionalized with an allyl substituent at C-2 following Buchi's procedure.[16] Thus, compound **5** was treated with of *n*-BuLi (1.5 equiv) at −10 °C followed by subsequent additions of anhydrous CuI and allyl bromide, which upon acidic workup (aqueous oxalic acid) provided **6** in 96% yield. The phenolic function of **6** was protected again with the *t*-butyldimethylsilyl group (TBS) following standard literature procedures,[17] affording compounds **7** in 83% yield. Finally, the oxidative cleavage of the terminal double bond with $KMnO_4$ and H_5IO_6 in a mixture of isopropanol/water afforded aldehyde **8** in 68% yield.[18]



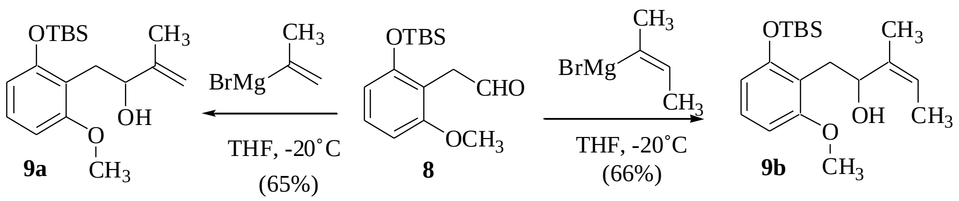
Scheme 1.

Aldehyde **8** was treated with the Grignard reagents derived from 2-bromopropene or *trans*-2-bromobutane providing the required allyl alcohols **9a** and **9b** for the Claisen–Johnson protocol in 65% and 66% yield, respectively (Scheme 2).

When alcohols **9** were subjected to the Claisen–Johnson conditions with a variety of ortho esters **10** in xylenes at 145 °C and in the presence of catalytic amount of propionic acid, the γ,δ-unsaturated esters **12** were obtained in very good yields (Table 1). In our first experiment (entry 1), alcohol **9a** ($R_2 = H$) and ortho ester **10** ($R_1 = H$) afforded **12a** in 95% yield.

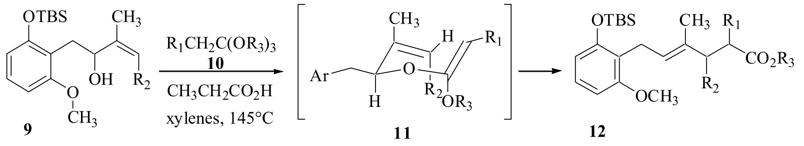
Analysis of Table 1 reveals that the synthesis of the α-esters **12b–d** was accomplished by introduction of the appropriate R_1 substituent in the ortho ester **10** used (Table 1, entries 2–4). Therefore, when the reaction was carried out with alcohol **9a** ($R_2 = H$) and the corresponding substituted ortho esters **10** ($R_1 = CH_3$, C_2H_5, Cl), the side chain of **12b–d** already containing the α-substituent was assembled in a direct manner and in very good yields. Reports on the use of heteroatom substituted ortho esters in the Johnson protocol are rare in the literature. Daub et al.[19] has shown that trimethyl methoxy orthoacetate participates in the Claisen reaction producing α-methoxy-γ,δ-unsaturated esters in reasonable yields. In this regard, it is noteworthy to mention that the use of trimethyl chloro ortho ester **10** (R = Cl, entry 4) represents another example of a heteroatom substituted ortho ester as a partner in the Claisen–Johnson procedure that allows the introduction of a chlorine group at the α-position of ester **12d**.

The synthesis of the β-methylated ester **12e** (Table 1, entry 5) was performed using alcohol **9b** ($R_2 = CH_3$) and ortho ester **10** ($R_1 = H$) in the same manner. When these compounds were heated in xylenes at 145 °C in the presence of a catalytic amount of propionic acid as before, afforded **12e** in 69% yield. Finally, the α,β-dimethylated ester **12f** (entry 6) was prepared using aldehyde **9b** ($R_2 = CH_3$) and ortho ester **10e** ($R_1 = CH_3$) under exactly the same conditions affording ester **12f** in 85% yield. According to literature precedents,[20] the (*Z*)-geometry of the double bond in the allyl alcohol **9b** used, provides **12f** with an *anti* arrangement of the methyl groups at the α- and β-positions. The relative stereochemistry of these centers was confirmed on the basis of an X-ray crystal structure of acid **4e**, obtained by removal of the phenolic protecting



Scheme 2.

Table 1. Claisen–Johnson reaction of allyl alcohols **9** with orthoacetates **10**



Entry	Ester R_3	Allyl alcohol R_2	Ortho ester R_1	Yield (%)
1	C_2H_5	H	H	**12a** (95)
2	C_2H_5	H	CH_3	**12b** (89)
3	CH_3	H	C_2H_5	**12c** (69)
4	CH_3	H	Cl	**12d** (98)
5	C_2H_5	CH_3	H	**12e** (69)
6	C_2H_5	CH_3	CH_3	**12f** (85)

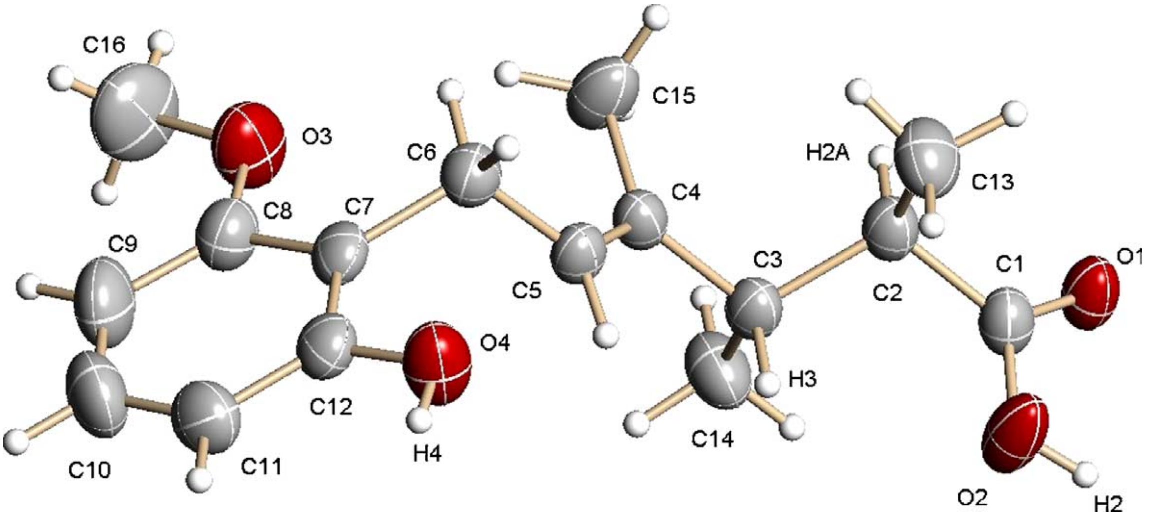
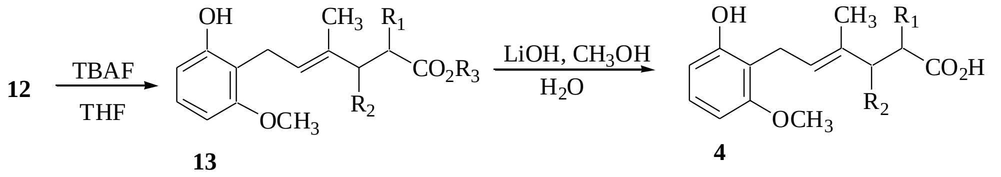


Figure 1. X-ray structure of compound **4e**.

group and base hydrolysis of the ester function (Fig. 1) in which the *anti* arrangement of the methyl groups can be seen.[21] The (*E*)-geometry of the double bond on compound **12f** is the result of a cyclic transition state in a chair conformation derived from **11** where the [3, 3] sigmatropic event takes place,[22] we assume the same geometry for all compounds **12**. We have also utilized the Claisen–Johnson rearrangement protocol in the synthesis of β-alkylated analogues of MPA possessing exactly the same side chain where the (*E*)-geometry has also been corroborated by X-ray diffraction studies.[23]

In the last steps of our sequence (Scheme 3), removal of the phenolic TBS protecting group on compounds **12** was carried out with tetra *n*-butylammonium fluoride (TBAF) in THF to obtain esters **13**, followed by hydrolysis of the ester functionality under the usual saponification conditions (LiOH in water–methanol mixtures),



13a $R_1 = R_2 = H, R_3 = Et$ (95%)
13b $R_1 = CH_3, R_2 = H, R_3 = Et$ (99%)
13c $R_1 = C_2H_5, R_2 = H, R_3 = Me$ (85%)
13d $R_1 = Cl, R_2 = H, R_3 = Me$ (72%)
13e $R_1 = H, R_2 = CH_3, R_3 = Et$ (85%)
13f $R_1 = CH_3, R_2 = CH_3, R_3 = Et$ (75%)

4a $R_1 = R_2 = H$ (78%)
4b $R_1 = CH_3, R_2 = H$ (76%)
4c $R_1 = C_2H_5, R_2 = H$ (66%)
4d $R_1 = H, R_2 = CH_3$ (68%)
4e $R_1 = CH_3, R_2 = CH_3$ (80%)

Scheme 3.

affording acids **4** in yields ranging from 60% to 80%, except in the case of the chlorinated derivative **13d**, where a complex mixture of products was observed.

We investigated the cytotoxic effect of the 11 monocyclic analogues (**13a–f** and **4a–e**) of MPA on the growth of 259Q and BMK/16-myc[24] cells using MTT (1-(4,5-dimethylthiazol-2yl)-3,5-diphenylformazan) assay, (1 nM, 10 nM, 100 nM, 1 μM, 10 μM, 100 μM, 1 mM). Unfortunately, none of the analogues tested showed cytotoxicity against these cells lines. We believe that the absence of any cytotoxic effect in these analogues may be due mainly to the lack of the lactone ring and to a lesser extent to the absence of the methyl group at C-4 in the aromatic ring. Although in previous reports[10] it was observed that modification of these structural features lead to a diminished or even loss in the biological activity of mycophenolic acid analogues, on the other hand, Anderson et al.[11] and particularly Lai and Anderson[12] report some promising anticancer activity in one of his monocyclic carboxamide analogues lacking these groups.

3. Conclusions

In conclusion, the synthetic scope of the Claisen–Johnson protocol has been extended since α-, β-, and α,β-disubstituted derivatives can be prepared from a single aldehyde precursor by appropriate choice of the R_1 group in the ortho ester used in the Claisen protocol, the appropriate R_2 group in the Grignard reagent used to prepare allylic alcohols **9** and combinations of both. However, none of the 11 analogues prepared with this methodology showed significant anticancer activity in the cell lines used.

4. Experimental

IR spectra were obtained using a Brucker vector 22 FT-IR spectrometer; NMR spectra were recorded on a Mercury-2000 and Inova Varian spectrometer at 200 and 400 MHz for ^{1}H and 50 and 100 MHz for ^{13}C. Unless otherwise specified, $CDCl_3$ was used as a solvent. Gas chromatography–mass spectra analyses were performed on an Agilent 6890 series equipped with an electronic impact mass detector Agilent 5973N at 70 eV; HRMS data were obtained on a JEOL MStation JMS-700. Melting points were determined on a Fisher–Johns melting point apparatus. THF was distilled from Na-benzophenone immediately before use, and other solvents were purified using standard procedures. Flash column chromatography was carried out on silica gel (230–499 mesh) and thin layer chromatography was performed with silica gel 60 F_{254} plates.

4.1. 2-Allyl-3-methoxyphenol (6)

In a round bottomed flask equipped with a magnetic stirrer and under a nitrogen atmosphere, 52.16 g (250.43 mmol) of 2-(3-methoxyphenoxy)tetrahydro-2*H*-pyrane,[25] was dissolved in 530 mL of anhydrous THF, at a temperature between −10 and 0 °C. Then, 250 mL (375.68 mmol) of a 1.5 M solution of *n*-butyllithium in hexanes was added. The reaction mixture was stirred at room temperature for 10 h and after this period of time, 22.65 g (118.95 mmol) of anhydrous CuI was added. After stirring at room temperature for 1 h, the reaction mixture was again cooled between −10 and 0 °C and 45.45 g (375.68 mmol) of allyl bromide was added. The solution was stirred at room temperature for 1 h, heated at reflux for 2 h, cooled to ambient temperature and poured into a flask containing 300 mL of water. The resulting mixture was filtered through a bed of Celite and extracted with ethyl acetate (3× 300 mL). The combined organic extracts were washed with 300 mL of saturated aqueous NH_4Cl, dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The product was redissolved in 1.0 L of a 90% aqueous methanolic solution and treated with 5.25 g (58.31 mmol) of oxalic acid. At the end of this procedure, the solvent was removed in vacuo, and the crude product dissolved in 300 mL of ethyl acetate. The organic solution was washed with 300 mL of water and the aqueous phase extracted with ethyl acetate (3× 300 mL), the organic phases were combined, washed with 300 mL of water, dried over Na_2SO_4 and the solvent in vacuo to give the crude product. Flash chromatography (hexane/ethyl acetate, 9:1) gave 39.53 g (96%) of the product as a red oil.

^{1}H NMR (200 MHz) δ 7.07 (t, J = 8.2 Hz, 1H), 6.49 (d, J = 8.2 Hz, 2H), 5.98 (m, J = 10.0, 6.0, 1.8 Hz, 1H), 5.32 (s, 1H), 5.11 (dq, J = 10.0, 1.8 Hz, 1H), (5.04, q, J = 1.8 Hz, 1H), 3.80 (s, 3H), 3.46 (dt, J = 6.0, 1.8 Hz, 2H). IR (thin film) 3443, 2942, 2839, 1599, 1469 cm^{-1}. MS (EI) *m*/*z* 164 (M$^+$).

4.2. 2-Allyl-1-*O*-*tert*-butyldimethylsilyloxy-3-methoxybenzene (7)

2-Allyl-3-methoxyphenol, **6** (4.15 g, 23.04 mmol) was dissolved in 45 mL of *N*,*N*-dimethylformamide, under a nitrogen atmosphere at room temperature, then, 2.32 g (34.13 mmol) of imidazole was added. The mixture was stirred at room temperature for 10 min and 5.30 g (35.14 mmol) of *tert*-butyldimethyl silyl chloride was added and the stirring was continued for 8 h. The mixture was then poured into 50 mL of water, extracted with ethyl acetate (3× 50 mL). The combined organic extracts were washed with water (4× 100 mL), dried over Na_2SO_4 and the solvent removed in vacuo to give the crude material. Flash column chromatography (hexane/ethyl acetate, 9:1) gave 5.84 g (83%) of the product as a colorless oil. ^{1}H NMR (200 MHz) δ 7.04 (t, J = 8.0 Hz, 1H), 6.49 (t, J = 8.0, 2.0 Hz, 2H), 5.94 (m, J = 11.0, 6.0, 1.8 Hz, 1H), 4.96 (dq, J = 7.4, 1.8 Hz, 1H), 4.90 (t, J = 1.8 Hz, 1H), 3.78 (s, 3H), 3.40 (dt, J = 6.0, 1.8 Hz, 2H), 1.00 (s, 9H), 0.22 (s, 6H). IR (thin film) 2930, 2896, 2858, 1593, 1469 cm^{-1}. MS (EI) *m*/*z* 278 (M$^+$).

4.3. (2-*O*-*tert*-Butyldimethylsilyloxy-6-methoxyphenyl)-acetaldehyde (8)

To a solution of 61 g (219 mmol) of 2-allyl-1-o-*tert*-butyldimethylsilyloxy-3-methoxybenzene (**7**) dissolved in 840 mL of isopropanol 96.9 g (613.4 mmol) of $KMnO_4$ previously dissolved in 350 mL of water was added slowly. The reaction course was followed by thin layer chromatography (hexane/ethyl acetate, 9:1) until disappeareance of the starting material. At this point, 109.8 g (481.9 mmol) of H_5IO_6, dissolved in 100 mL of water was added. When the reaction was over (TLC), the mixture was poured into 500 mL of water, extracted with ethyl acetate (3× 500 mL) and the combined extracts washed with $NaHCO_3$ (4× 500 mL) until pH 7. The organic phase was dried (Na_2SO_4) and the solvent removed. Flash column chromatography (hexane/ethyl acetate, 9:1) gave 42.02 g (68%) of the product as a yellow oil. ^{1}H NMR (400 MHz) δ 9.37 (t, *J* = 2.0 Hz, 1H), 6.91 (t, *J* = 8.4 Hz, 1H), 6.32 (ddd, *J* = 8.4, 1.2 Hz, 2H), 3.57 (s, 3H), 3.44 (d, *J* = 2.0 Hz, 2H), 0.76 (s, 9H), 0.1 (s, 6H). IR (thin film) 2957, 2935, 2895, 2860, 1728, 1594, 1471 cm^{-1}. MS (EI) *m*/*z* 280 (M$^+$).

4.4. General procedure for the preparation of allyl alcohols (9a) and (9b)

In a round bottomed flask equipped with a magnetic stirrer, a condenser and under a nitrogen atmosphere, 1.5 equiv of metalic magnesium (previously dried), 90 mL of anhydrous THF, 1.0 equiv of the corresponding vinyl halide (2-bromopropene or *trans*-2-bromobutene) and a catalytic amount of iodine were added and the resulting mixture heated at reflux until the magnesium was consumed (5 h). In a separate flask, 1.0 equiv of (2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)acetaldehyde (**8**) was dissolved in 65 mL of anhydrous THF. The solution was cooled to −10 °C and the Grignard reagent previously prepared was added dropwise. The mixture was stirred at this temperature until the presence of the product was detected (TLC, hexane/ethyl acetate, 9:1). The reaction mixture was quenched with 30 mL of a saturated aqueous solution of NH_4Cl and 70 mL of ethyl acetate. The aqueous phase was extracted with ethyl acetate (3× 100 mL) and the combined extracts were washed with 100 mL of brine, dried over Na_2SO_4 and the solvent removed. The resulting allyl alcohols were purified by flash column chromatography (hexane/ethyl acetate, 9:1).

4.4.1. 1-(2-*O*-*tert*-Butyldimethylsilyloxy-6-methoxyphenyl)-3-methylbut-3-en-2-ol (9a). Yield: 3.0 g (65%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.06 (t, *J* = 8.0 Hz, 1H), 6.5(ddd, *J* = 38.0, 0.4 Hz, 2H), 5.00 (t, *J* = 1.4 Hz, 1H), 4.82 (t, *J* = 1.4 Hz, 1H), 4.22 (td, *J* = 9.6, 4.0, 1.0 Hz, 1H), 3.82 (s, 3H), 2.99 (dd, *J* = 13.6, 3.2 Hz, 2H), 2.87 (dd, *J* = 13.6, 9.6 Hz, 2H), 2.75 (d, *J* = 4.0 Hz, 1H), 1.84 (s, 3H), 1.01 (s, 9H), 0.26 (d, *J* = 6.0 Hz, 6H). IR (thin film) 3563, 3078, 2934, 2893, 2860, 1592, 1469 cm^{-1}. MS (EI) *m*/*z* 322 (M$^+$).

4.4.2. 1-(2-*O*-*tert*-Butyldimethylsilyloxy-6-methoxyphenyl)-3-methylpent-3-en-2-ol (9b). Yield: 3.60 g (66%) as a yellow oil. ^{1}H NMR (200 MHz) δ 7.03 (t, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 8.0, 4.8 Hz, 2H), 5.25 (qquint, *J* = 7.0, 1.0 Hz, 1H), 4.77 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.79(s, 3H), 2.91 (m, *J* = 13.2, 9.2, 4.0 Hz, 2H), 1.79 (quint, *J* = 1.0 Hz, 3H), 1.53 (dq, *J* = 7.0, 1.0 Hz, 3H), 1.02 (s, 9H), 0.25 (d, *J* = 5.4 Hz, 9H). IR (thin film) 34689, 2934, 2860, 1591, 1469 cm^{-1}. MS (EI) *m*/*z* 337 (M$^+$).

4.5. General procedure for the Claisen–Johnson reactions

In a round bottomed flask equipped with stirrer, a vigreux column and a thermometer, 1.0 equiv of the allyl alcohols (**9a** and **9b**), 10.0 equiv of the ortho esters (**10**) and 0.4 equiv of propionic acid were dissolved in 15 mL of xylenes. The reaction mixture was heated in an oil bath at 145 °C, until the reaction was complete (TLC). The solvent was evaporated and the crude products then obtained were purified by flash column chromatography (hexane/ethyl acetate, 9:1).

4.5.1. Ethyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-4-methylhex-4-enoate (12a). Yield: 3.28 g (90%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.00 (t, *J* = 8.0 Hz, 1H), 6.45 (ddd, *J* = 8.0, 0.8 Hz, 2H), 5.20 (td, *J* = 6.8, 1.4 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.33 (d, *J* = 6.8 Hz, 2H), 2.36 (m, *J* = 6.8, 4.4, 1.4 Hz, 2H), 2.27 (m, *J* = 6.8, 4.4 Hz, 3H), 1.75 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.00 (s, 9H), 0.23 (s, 6H). IR (thin film) 2957, 2934, 2860, 1737, 1592, 1469 cm^{-1}. MS (EI) *m*/*z* 392 (M$^+$).

4.5.2. Ethyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-2,4-dimethylhex-4-enoate (12b). Yield: 4.71 g (89%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.00 (t, *J* = 8.0 Hz, 1H), 6.47 (ddd, *J* = 8.0, 0.8 Hz, 2H), 5.20 (td, *J* = 6.8, 1.2 Hz, 1H), 4.02 (c, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.32 (d, *J* = 6.8 Hz, 2H), 2.57 (m, *J* = 8.0, 7.0 Hz, 2H), 2.34 (ddd, *J* = 13.2, 7.0, 0.8 Hz, 1H), 1.99 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.73 (d, *J* = 0.8 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H) 1.00 (s, 9H), 0.26 (s, 6H). ^{13}C NMR (100 MHz) 177.0, 158.9, 154.3, 131.6, 126.5, 126.1, 120.8, 111.8, 103.9, 60.2, 55.8, 44.2, 38.2, 26.0, 23.0, 18.5, 16.6, 16.0, 14.4, −3.9. IR (thin film) 2956, 2934, 2859, 1734, 1591, 1468 cm^{-1}. MS (EI) *m*/*z* 349; 303. (M$^+$).

4.5.3. Methyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-2-ethyl-4-methylhex-4-enoate (12c). Yield: 0.85 g (69%) as a yellow oil. ^{1}H NMR (200 MHz) δ 6.97 (t, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 8.0, 0.8 Hz, 2H), 5.17 (td, *J* = 7.0, 1.2 Hz, 1H), 3.76 (s, 3H), 3.50 (s, 3H), 3.30 (d, *J* = 7.0 Hz, 2H), 2.44 (m, *J* = 8.0, 7.0, 3.0, 1.6 Hz, 1H), 2.24 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.06 (dd, *J* = 13.2, 7.0 Hz, 1H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.50 (m, *J* = 7.2, 6.0, 3.0, 1.6 Hz, 2H), 1.00 (s, 9H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.24 (s, 6H). ^{13}C NMR (50 MHz, CDCll) δ 1776.3, 158.6, 154.0, 131.5, 126.2, 125.7, 120.6, 111.6, 103.8, 55.8, 51.3, 46.2, 42.9, 26.2, 23.2, 18.7, 16.3, 12.0, −3.6. IR (thin film) 2958, 2933, 2859, 1738, 1592, 1469 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{38}O_4Si$: 406.2539. Found: 406.2522.

4.5.4. Methyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-2-chloro-4-methylhex-4-enoate (12d). Yield: 2.52 g (98%) as a reddish oil. ^{1}H NMR (200 MHz) δ 6.98 (t, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 8.0, 0.8 Hz, 2H), 5.29 (td, *J* = 7.0, 1.2 Hz, 1H), 4.33 (t, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.69 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.49 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.77 (s, 3H), 1.00 (s, 9H), 0.23 (s, 6H). IR (thin film) 2955, 2932, 2858, 1750, 1592, 1469 cm^{-1}. MS (EI) *m/z* 413 (M$^+$).

4.5.5. Ethyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-3,4-dimethylhex-4-enoate (12e). Yield: 5.01 g (69%) as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.00 (t, *J* = 8.4 Hz, 1H), 6.47 (ddd, *J* = 8.4, 0.8 Hz, 2H), 5.20 (td, *J* = 6.8, 1.2 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.31 (d, *J* = 6.8 Hz, 2H), 2.58 (m, *J* = 14.0, 8.0, 6.8 Hz, 1H) , 2.37 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.18 (dd, *J* = 14.0, 8.0 Hz, 1H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H). IR (thin film) 2958, 2931, 2858, 1735, 1592, 1470 cm^{-1}. MS (EI) *m/z* 406 (M$^+$).

4.5.6. Ethyl-(4*E*)-6-(2-*O*-*tert*-butyldimethylsilyloxy-6-methoxyphenyl)-2,3,4-trimethylhex-4-enoate (12f). Yield: 5.29 g (85%) as a yellow oil . ^{1}H NMR (400 MHz) δ 7.02 (t, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.4 Hz, 2H), 5.25 (td, *J* = 6.8, 1.2 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.35 (d, *J* = 6.8 Hz, 2H), 2.29 (m, *J* = 6.8, 3.6 Hz, 2H), 1.63 (d, *J* = 1.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.02 (s, 9H), 0.97 (dd, *J* =6.6 Hz, 6H), 0.24 (s, 6H). ^{13}C NMR (100 MHz) δ 177.2, 159.1, 154.3, 135.4, 126.5, 126.0, 121.0, 111.8, 104.0, 60.2, 55.8, 46.7, 44.0, 26.0, 22.7, 18.5, 18.2, 16.5, 14.5, 12.0, −3.9. IR (thin film) 2961, 2935, 2861, 1733, 1592, 1469 cm^{-1}. MS (EI) = *m/z* 420 (M$^+$). HRMS (EI) calcd for $C_{24}H_{40}O_4Si$: 420.2696. Found: 420.2485.

4.6. General procedure for the deprotection of the phenolic functions

To 1.0 equiv of compounds (**12a** to **12f**) dissolved in 30 mL of anhydrous THF at 0 °C, 19.1 mmol of a 1 M solution of *n*-tetrabutyl ammoniun fluoride was added. The reaction was monitored by thin layer chromatography (hexane/ethyl acetate, 9:1), until the starting materials has disappeared, then 10 mL of an aqueous saturated NH_4Cl was added. The mixture was extracted with ethyl acetate (3× 40 mL), washed with 40 mL of brine, dried over Na_2SO_4 and the solvent evaporated. The products obtained were purified using flash column chromatography (hexane/ethyl acetate, 9:1).

4.6.1. Ethyl-(4*E*-)6-(2-hydroxy-6-methoxyphenyl)-4-methyhex-4-enoate (13a). Yield: 1.69 g (95%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.05 (t, *J* = 8.0 Hz, 1H), 6.47 (dd, *J* = 8.0, 2.8 Hz, 2H), 5.26 (td, *J* = 7.2, 1.2 Hz, 1H), 5.11 (s, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.40 (d, *J* = 7.2 Hz, 2H), 2.42 (m, *J* = 6.9, 2.0, 1.2 Hz, 2H), 2.33 (m, *J* = 8.4, 6.8 Hz, 2H), 1.81 (d, *J* = 1.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 mHz) δ 173.6, 158.2, 155.4, 135.8, 127.3, 123.1, 115.4, 109.1, 103.3, 60.6, 56.0, 34.9, 33.2, 22.3, 16.3, 14.4. IR (thin film) 3423, 2984, 2936, 1709, 1600, 1468 cm^{-1}. MS (EI) *m/z* 278 (M$^+$). HRMS (EI) calcd for $C_{16}H_{22}O_4$: 278.1518. Found: 278.1536.

4.6.2. Ethyl-(4*E*)-6-(2-hydroxy-6-methoxyphenyl)-2,4-dimethylhex-4-enoate (13b). Yield: 3.28 g (99%) as a slightly yellow solid, mp 55–56 °C. ^{1}H NMR (400 MHz) δ 7.04 (t, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 1.2 Hz, 2H), 5.25 (td, *J* = 7.2, 0.8 Hz, 1H), 5.15 (s, 1H), 4.05 (q, *J* = 6.8 Hz, 2H), 3.79 (s, 3H), 3.39 (d, *J* = 7.2 Hz, 2H), 2.62 (m, *J* = 14, 7.6, 6.8 Hz, 1H), 2.37 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.06 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.79 (d, *J* = 0.8 Hz, 3H), 1.19 (t, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz) δ 176.6, 158.1, 155.3, 134.4, 127.2, 124.7, 115.4, 109.0, 103.3, 60.5, 56.0, 44.2, 38.3, 22.4, 17.0, 16.2, 14.5. IR (thin film) 3425, 2976, 2936, 1707, 1599, 1468 cm^{-1}. MS (EI) *m/z* 292 (M$^+$). HRMS (EI) calcd for $C_{17}H_{24}O_4$: 292.1675. Found: 292.162.

4.6.3. Methyl-(4*E*)-6-(2-hydroxy-6-methoxyphenyl)-2-ethyl-4-methylhex-4-enoate (13c). Yield: 0.52 g (85%) as a beige solid, mp 46–47 °C. ^{1}H NMR (200 MHz) δ 7.04 (t, *J* = 8.2 Hz, 1H), 6.44 (dd, *J* = 8.2 Hz, 2H), 5.22 (tq, *J* = 7.0, 1.2 Hz, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 3.37 (d, *J* = 7.0 Hz, 2H), 2.49 (m, *J* = 8.8, 6.0, 3.0 Hz, 1H), 2.20 (m, *J* = 13.6, 8.8, 6.0 Hz, 1H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.56 (m, *J* = 7.5, 3.0 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (50 MHz) δ 176.3, 158.0, 155.1, 134.1, 127.0, 124.5, 115.5, 108.9, 103.2, 56.0, 51.6, 46.3, 42.9, 25.6, 22.6, 16.4, 12.3. IR (thin film) 3296, 2957, 2936, 2872, 1700, 1599, 1470 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{24}O_4$: 292.1675. Found: 292.162.

4.6.4. Methyl-(4*E*)-6-(2-hydroxy-6-methoxyphenyl)-2-chloro-4-methylhex-4-enoato (13d). Yield: 1.53 g (72%) as a yellow oil. ^{1}H NMR (200 MHz) δ 6.98 (t, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 8.2, 3.2 Hz, 2H), 5.53 (s, 1H), 5.34 (tq, *J* = 7.4, 0.8 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 3.37 (d, *J* = 7.4 Hz, 2H), 2.70 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.53 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.80 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (50 MHz) δ 170.1, 158.1, 154.7, 130.0, 127.8, 127.0, 115.2, 108.7, 103.2, 55.9, 55.6, 53.0, 45.4, 22.6, 16.2. IR (thin film) 3452, 2953, 2839, 1739, 1598, 1469 cm^{-1}. MS (EI) *m/z* 298 (M$^+$). HRMS (EI) calcd for $C_{15}H_{19}O_4Cl$: 298.0972. Found: 298.0968.

4.6.5. Ethyl-(4*E*)-6-(2-hydroxy-6-methoxyphenyl)-3,4-dimethylhex-4-enoato (13e). Yield: 2.9 g (85%) as a yellow oil. ^{1}H NMR (200 MHz) δ 7.02 (t, *J* = 8.4 Hz, 1H), 6.46 (dd, *J* = 8.4, 2.2 Hz, 2H), 5.28 (t, *J* = 6.8 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 3.39 (d, *J* = 6.8 Hz, 2H), 2.64 (m, *J* = 14.4, 6.8 Hz, 1H), 2.39 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.28 (m, *J* = 14.4, 7.6 Hz, 1H), 1.76 (d, *J* = 0.8 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). IR (thin film) 3418, 2965, 2840, 171, 1600, 1469 cm^{-1}. MS (EI) 292 *m/z* (M$^+$). HRMS (EI) calcd for $C_{17}H_{24}O_4$: 292.1675. Found: 292.1646.

4.6.6. Ethyl-(4*E*)-6-(2-hydroxy-6-methoxyphenyl)-2,3,4-trimethylhex-4-enoate (13f). Yield: 1.92 g (75%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.03 (t, *J* = 8.2 Hz, 1H), 6.45 (dd, *J* = 8.2 Hz, 2H), 5.30 (tq, *J* = 7.0, 1.4 Hz, 1H), 4.12 (q, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), 3.40 (d, *J* = 7.0 Hz, 2H), 2.34 (m, *J* = 10.2, 6.4 Hz, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.24 (t *J* = 7.4 Hz, 3H), 0.99 (dd, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz) δ 176.8, 158.2, 155.3, 138.4, 127.2, 124.5, 115.3, 108.9, 103.3, 60.4, 55.9, 46.7, 43.9, 22.2, 18.2, 16.6, 14.5, 12.3. IR (thin film)

3426, 2972, 2935, 1705, 1600, 1468 cm^{-1}. MS (EI) 306 *m/z* (M^{+}). HRMS (EI) calcd for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1843.

4.7. General procedure for the basic hydrolysis

To 1.0 equiv of esters (**13a** to **13f**) dissolved in 36 mL of a 4:1 mixture of THF:ethanol, were added 4.0 eq of LiOH previously dissolved on 5 mL of water. When the reaction was completed (TLC), the solvent was evaporated and the residue was dissolved in 30 mL of water, acidified to pH 1 with 10% aqueous HCl and extracted with ethyl acetate (3× 40 mL). The organic phases were dried (Na_2SO_4) and the solvent was evaporated. The products were purified using flash column chromatography (hexane/ethyl acetate, 8:2).

4.7.1. (4*E*)-6-(2-Hydroxy-6-methoxyphenyl)-4-methyhex-4-enoic acid (4a). Yield: 1.27 g (78%) as yellow solid, mp 62–63 °C. ^{1}H NMR (400 MHz) δ 7.03 (t, $J = 8.0$ Hz, 1H), 6.45 (dd, $J = 8.0$, 3.6 Hz, 2H), 5.27 (td, $J = 6.8$ Hz, 1H), 4.47 (s, 1H), 3.80 (s, 3H), 3.40 (d, $J = 6.8$ Hz, 2H), 2.42 (m, $J = 6.9$, 2.0, 1.2 Hz, 2H), 2.33 (m, $J = 8.4$, 6.8 Hz, 2H), 1.81 (d, $J = 1.2$ Hz, 3H), 1.21 (t $J = 7.2$ Hz, 3H). IR (thin film) 3409, 2924, 1711, 1601, 1467 cm^{-1}. MS (EI) 250 *m/z* (M^{+}). HRMS (EI) calcd for: $C_{17}H_{24}O_4$ 250.1205. Found: 250.1245.

4.7.2. (4*E*)-6-(2-Hydroxy-6-methoxyphenyl)-2,4-dimethyhex-4-enoic acid (4b). Yield: 1.72 g (76%) as a yellow solid, mp 81–82 °C. ^{1}H NMR (200 MHz) δ 6.70 (t, $J = 8.0$ Hz, 1H), 6.43 (dd, $J = 8.0$, 3.0 Hz, 2H), 5.28 (t, $J = 7.0$ Hz, 1H), 3.78 (s, 3H), 3.38 (d, $J = 7.0$ Hz, 2H), 2.64 (m, $J = 14.0$, 7.0 Hz, 1H), 2.40 (dd, $J = 14.0$, 7.0 Hz, 1H), 2.06 (dd, $J = 14.0$, 7.0 Hz, 1H), 1.78 (s, 3H), 1.10 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (50 MHz) δ 182.1, 158.0, 155.0, 133.6, 127.1, 125.1, 115.5, 108.9, 103.3, 56.0, 44.0, 38.1, 22.6, 16.8, 16.2. IR (thin film) 3406, 2977, 2935, 1706, 1598, 1468 cm^{-1}. MS (EI) = 264 *m/z* (M^{+}). HRMS (EI) calcd for $C_{15}H_{20}O_4$: 264.1362. Found: 264.1358.

4.7.3. (4*E*)-6-(2-Hydroxy-6-methoxyphenyl)-2-ethy-4-methyhex-4-enoic acid (4c). Yield: 0.24 g (66%) as an orange oil. ^{1}H NMR (200 MHz) δ 7.00 (t, $J = 8.0$ Hz, 1H), 6.43 (dd, $J = 8.0$, 2.0 Hz, 2H), 5.27 (t, $J = 6.6$ Hz, 1H), 3.77 (s, 3H), 3.38 (d, $J = 7.0$ Hz, 2H), 2.49 (m, $J = 8.0$, 6.6 Hz, 1H), 2.34 (dd, $J = 13.6$, 8.0 Hz, 1H), 2.16 (dd, $J = 13.6$, 6.6 Hz, 1H), 1.79 (s, 3H), 1.53 (m, $J = 7.6$, 6.6 Hz, 3H), 0.92 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (50 MHz) δ 181.3. 158.0, 155.0, 134.1, 127.1, 124.8, 115.4, 108.9, 103.3, 56.0, 45.9, 42.4, 25.3, 22.6, 16.4, 12.2. IR (thin film) 3408, 2965, 2936, 1705, 1597, 1469 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{22}O_4$: 278.1518. Found: 278.1530.

4.7.4. (4*E*)-6-(2-Hydroxy-6-metoxyphenyl)-3,4-dimethylhex-4-enoic acid (4d). Yield: 1.22 (68%) as a colorless oil. ^{1}H NMR (200 MHz) δ 7.02 (t, $J = 8.2$ Hz, 1H), 6.44 (dd, $J = 8.2$, 2.0 Hz, 2H), 5.30 (t, $J = 7.0$ Hz, 1H), 3.78 (s, 3H), 3.9 (d, $J = 7.0$ Hz, 2H), 2.64 (m, $J = 14.6$, 7.6, 6.6 Hz, 1H), 2.45 (dd, $J = 14.6$, 7.6 Hz, 1 H), 2.29 (dd, $J = 14.6$, 7.6 Hz, 1 H), 1.77 (s, 3H), 1.07 (d, $J = 6.6$ Hz, 3H). IR (thin film) 3394, 2977, 2938, 1707, 1599, 1468 cm^{-1}. MS (EI) = *m/z* 264 (M^{+}). HRMS (EI) calcd for: $C_{15}H_{20}O_4$ 264.1362. Found: 264.1341.

4.7.5. (4*E*)-6-(2-Hydroxy-6-methoxyphenyl)-2,3,4-trimethylhex-4-enoic acid (4e). Yield: 0.45 g (80%) as a redish solid, mp 110–111 °C. ^{1}H NMR (200 MHz) δ 7.03 (t, $J = 8.4$ Hz, 1H), 6.45 (dd, $J = 8.4$, 28 Hz, 2H), 5.31 (tq, $J = 7.0$, 1.2 Hz, 1H), 3.79 (s, 3H), 3.41 (d, $J = 7.0$ Hz, 2H), 2.36 (m, $J = 10.3$, 6.6 Hz, 2H), 1.69 (s, 3H), 1.05 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (50 MHz) δ 182.0, 158.4, 155.3, 138.1, 127.4, 124.9, 115.4, 109.0, 103.4, 56.0, 46.4, 43.6, 22.2, 18.1, 16.4, 12.3. IR (thin film) 3436, 2983, 2936, 1681, 1600, 1467 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{22}O_4$: 278.1518. Found: 278.1530.

4.8. In vitro assays

259Q and BMK cells were maintained in DMEM and DMEM F-12, respectively, and were grown at 37 °C in a 5% CO_2 atmosphere, 5×10^3 cells/well were inoculated in 95-well plates. Various doses of analogues were added to each well and inoculated for 24 h. Fifty microliters of MTT (5 mg/mL) was added and the plate was incubated for 4 h. The absorbance of MTT-formazan was measured using a 550 nm filter-equipped microplate reader (BIORAD Ultramark).

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