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PAPER

Synthesis and antitumor activity of inositol phosphotriester analogues†

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Inositol phosphates, as important second messengers of signal transduction, regulate many biological functions. However, cell penetration and phospholipase stability could be two main issues faced by inositol phosphate analogues used as lead compounds for drug discovery. Inositol phosphotriester analogues could be more beneficial to diffuse across plasma membrane. In this paper, we describe the design and synthesis of a series of inositol phosphotriester analogues based on phosphatidylinositol, along with the initial antitumor activity analysis. Several compounds exhibited good cytotoxic activity against human cancer cell lines A549, HepG2, MDA-MB-231 and HeLa, especially compound **33** was cytotoxic against all the four cancer cell lines with good IC_{50} values.

Introduction

Inositol phosphates, inositol pyrophosphates, and phosphatidylinositol phosphates comprise an extremely diverse signaling molecules family for which variations in biological properties lead to independent regulation of numerous key cellular processes.[1] In particular, inositol 1,4,5-trisphosphate ($InsP_3$), as ubiquitous intracellular second messenger, stimulates the release of calcium ions. This signaling molecule is generated through the hydrolysis of phosphatidylinositol 4,5-bisphosphate ($PtdInsP_2$) by the intracellular phosphatidylinositol-specific phospholipase C (PI-PLC), which also produces another important signaling lipid diacylglycerol (DAG). $InsP_3$-mediated Ca^{2+} release is relative to a plethora of subsequent signaling events, including cell proliferation, muscle contraction, apoptosis, and gene transcription.[2] Because of the biological importance as second messenger in the intracellular signal transduction, a lot of $InsP_3$ analogues have been synthesized, such as deoxy analogues, fluorinated analogues, ring-modified analogues, phosphorothioate analogues, phosphonate analogues, bicyclic analogues, conformationally restricted analogues and adenophostin mimic analogues, many of which could behave as $InsP_3$ receptor agonists or antagonists.[3] Synthetic inositol-containing natural products and analogues are invaluable for elucidating the complex biological activities. Furthermore, they are useful for the development of new molecular probes that can interfere with cellular processes and new drug leads discovery based on novel therapeutic targets.

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The signaling pathways regulated by inositol phosphates and phosphatidylinositol phosphates have become important cancer therapeutic targets. Significant evidence suggests that PI-PLC could be target for the development of antitumor drugs. Hyperactivation of PI-PLC exists in a number of human tumors.[4] The majority of human breast cancers have detectable PI-PLCγ immunoreactive protein compared to benign breast tissue.[5] Cytosolic PI-PLC activity was evidently increased in human non-small cell lung cancers and renal cell cancers.[6] In addition, the cellular signaling pathway of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), which regulates a number of important biological processes such as cell growth, proliferation, survival, and apoptosis, is commonly deregulated in many human cancers.[7] Hyperactivation of the PI3K cascade, including phosphatase and tensin homologue (PTEN) deactivation and PI3K activation mutations, exists in almost every form of human cancers, for example colon cancers, breast cancers, melanomas, brain cancers, and gastric cancers.[8] Moreover, the activation of PI3K/AKT/mTOR signaling pathway would result in the resistance of cancer cells to both targeted anticancer therapies and conventional cytotoxic agents.[9] Accordingly, considerable drug discovery efforts are ongoing, targeting several components of the signaling cascade with single or multiple target strategies.[8f,h,10]

To date, few studies have addressed the application of inositol phosphate and phosphatidylinositol phosphate analogues as inhibitors to show antitumor activity. Some analogues were designed to repress the PI3K-dependent signaling pathway (Fig. 1). Falasca group found Ins(1,3,4,5,6)P_5 could inhibit the growth of cancer cell by the competitive binding of the AKT pleckstrin homology (PH) domain.[11] They recently has demonstrated that 2-*O*-Bn-Ins(1,3,4,5,6)P_5 exhibits enhanced antitumor activity.[12] Perifosine, which has a similar structure to naturally occurring phospholipids, was shown to inhibit the growth of PC-3 prostate carcinoma cells, in which PTEN mutation

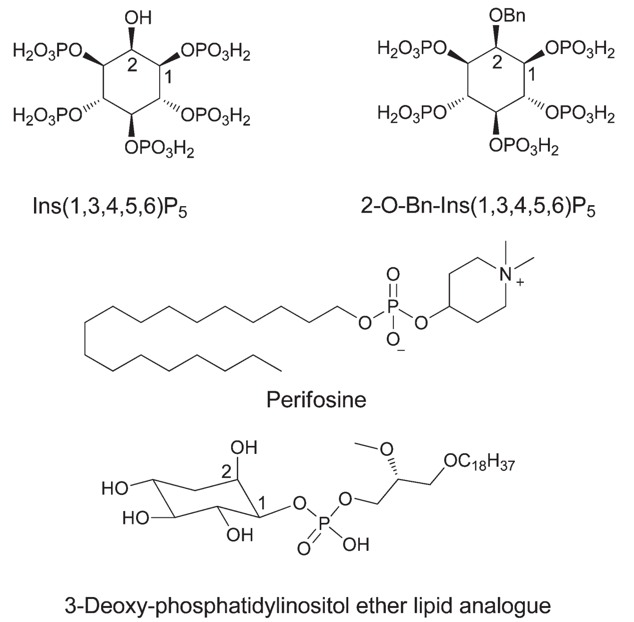


Fig. 1 Representative lipid-based antagonists of the PI3K pathway.

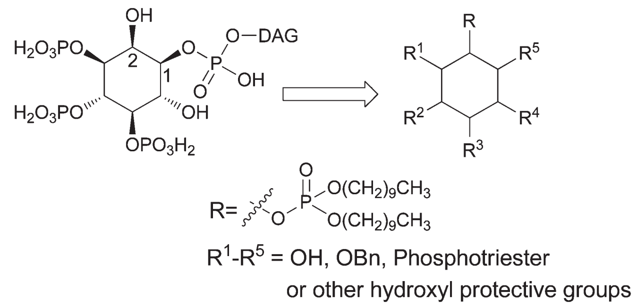
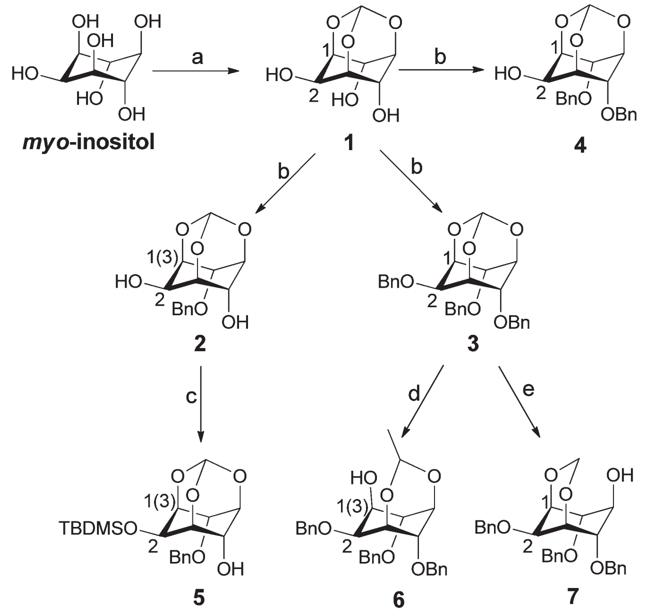


Fig. 2 The design concept of target molecules.



Scheme 1 Synthesis of mono-hydroxyl inositol compounds. Reagents and conditions: (a) $HC(OEt)_3$, PTSA monohydrate, DMF, 110 °C, 28 h, 83%; (b) NaH, BnBr, DMF, 0 °C–RT, overnight, 48% for **2**, 74% for **3**, 68% for **4**; (c) TBDMSCl, imidazole, DMF, RT, overnight, 90%; (d) $AlMe_3$, CH_2Cl_2, 0 °C–RT, 5 h, 68%; (e) DIBAL, CH_2Cl_2, 0 °C–RT, 4 h, 95%.

happened and the AKT pathway was highly activated.[13] Kozikowski's group found several 3-modified phosphatidylinositol analogues could block PI3K, AKT, and then repressed cancer cell growth.[14]

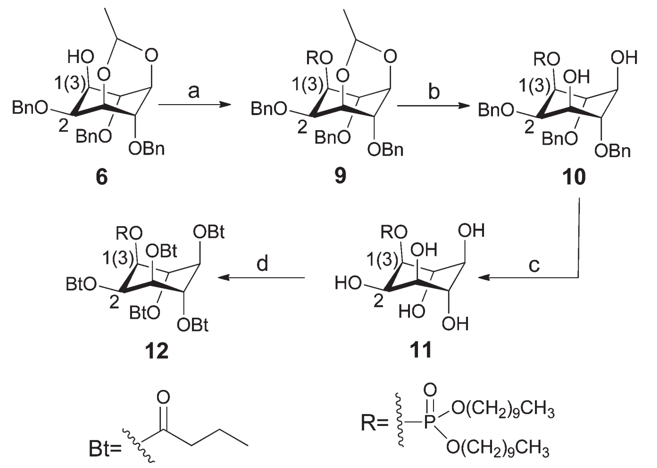
Cell penetration and phospholipase stability could be two main issues faced by inositol phosphate analogues used as lead compounds for drug discovery. The intrinsic charge associated with the phosphate groups of inositol phosphates renders these molecules unable to passively diffuse across the lipophilic cell membrane. If small molecules are to be truly useful as drug leads, they have to be readily membrane permeant. As the development is in its early stages, the structures of the analogues are similar to the natural products and often contain polar groups. Inositol phosphotriester analogues could be more beneficial to diffuse across plasma membrane.[15] However, little attention has been paid to inositol phosphotriester analogues to study their biological activities. In this paper, we reported the design and synthesis of a series of inositol phosphotriester analogues based on phosphatidylinositol, along with the initial antitumor activity analysis.

Results and discussion

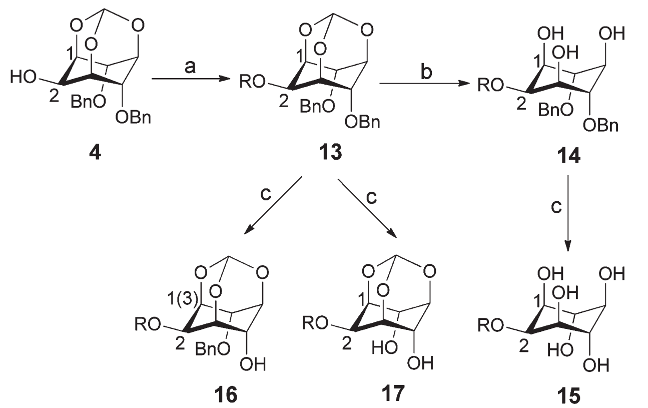
Synthesis

To try to improve the issues faced by inositol phosphate analogues used as drug leads, a series of inositol phosphotriester analogues of phosphatidylinositol were designed (Fig. 2). Firstly, DAG, as a second messenger, which could active PKC, plays important role in crucial biological function together with Ca^{2+}, and has contribution to the PI-PLC hydrolysis of phosphatidylinositol, so the lipophilic diacylglycerol (DAG) group was replaced with two decyl chains as phosphotriester to improve cell penetration and PI-PLC stability. Secondly, the DAG group is on the C1 position of *myo*-inositol in the natural phosphatidylinositol phosphates, however, *myo*-inositol is a meso-compound, each hydroxyl group has its own steric configuration, the phosphorylation occurred at different positions of *myo*-inositol, may lead to different stereo-configurations when interact with the target. Because Ins(1,3,4,5,6)P_5 and 2-*O*-Bn-Ins(1,3,4,5,6)P_5 exhibited good antitumor activity, some analogues also contained different numbers of benzyl groups or phosphotriester groups to enhance their interactions with the target through hydrogen bond or stacking.

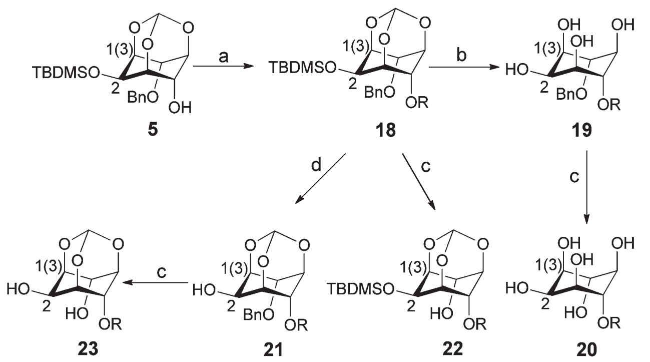
The mono-hydroxyl compounds **4**, **5**, **6** and **7** were synthesized using *myo*-inositol as starting material according to the route shown in Scheme 1. Treatment of *myo*-inositol with triethyl orthoformate in DMF provided the triol **1**.[16] Benzyl protection of the 2-, 4-, or 6-hydroxyl groups, the mono-hydroxyl compound **4**, the diol **2** and the total protected compound **3** were obtained respectively.[16b] The mono-hydroxyl compound **5** was afforded by the silylation of **2** with *tert*-butyldimethylsilyl chloride.[17] Selective ring-opening of **3** with trimethyl aluminium or diisobutylaluminium hydride gave **6** and **7**, respectively.[18]



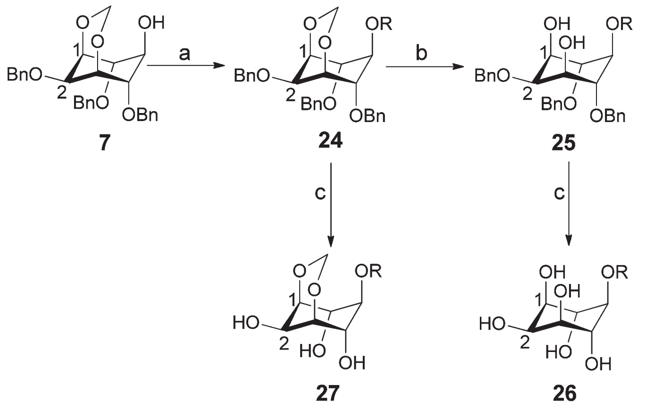
Scheme 2 Synthesis of 1(3)-phosphorylated analogues **9–12**. Reagents and conditions: (a) 1*H*-tetrazole, i-$Pr_2NP(OC_{10}H_{21})_2$ (**8**), CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 72%; (b) HCl, MeOH, RT, 2 h, 99%; (c) Pd–C, ethanol, RT, overnight, 93%; (d) Bt_2O, pyridine, RT, overnight, 90%.



Scheme 3 Synthesis of 2-phosphorylated analogues **13–17**. Reagents and conditions: (a) 1*H*-tetrazole, i-$Pr_2NP(OC_{10}H_{21})_2$ (**8**), CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 93%; (b) HCl, MeOH, RT–35 °C, 6 h, 75%; (c) Pd–C, ethanol, RT, overnight, 80% for **15**, 24% for **16**, 99% for **17**.



Scheme 4 Synthesis of 4(6)-phosphorylated analogues **18–23**. Reagents and conditions: (a) 1*H*-tetrazole, i-$Pr_2NP(OC_{10}H_{21})_2$ (**8**), CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 60%; (b) HCl, MeOH, RT-40 °C, 6 h, 95%; (c) Pd–C, ethanol, RT, overnight, 82% for **20**, 91% for **22**, 91% for **23**, (d) TBAF, THF, RT, 30 min, 98%.

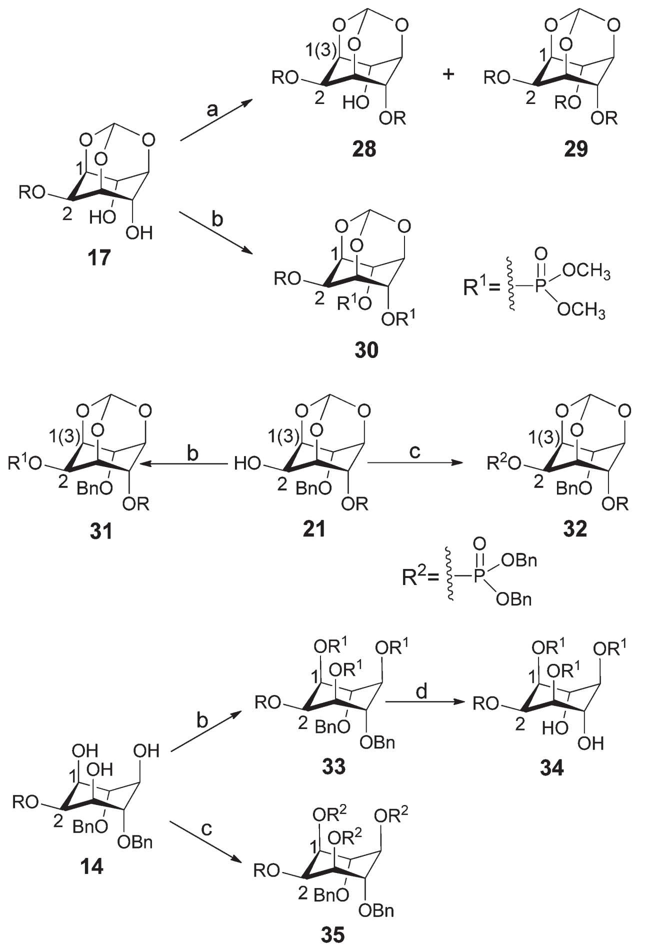


Scheme 5 Synthesis of 5-phosphorylated analogues **24–27**. Reagents and conditions: (a) 1*H*-tetrazole, i-$Pr_2NP(OC_{10}H_{21})_2$ (**8**), CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 86%; (b) HCl, MeOH, RT, 1 h, then reflux, 6 h, 80%; (c) Pd–C, ethanol, RT, overnight, 73% for **26**, 90% for **27**.

Phosphorylation of the mono-hydroxyl compounds **4**, **5**, **6**, **7** with **8** afforded **9**, **13**, **18**, **24** (Schemes 2–5), which were transformed into **16**, **17**, **22**, **27** employing catalytic hydrogenation. Acidic hydrolysis of compounds **9**, **13**, **18**, **24** provided **10**, **14**, **19** and **25**. Subsequently, hydrogenolytic removal of benzyl groups furnished **11**, **15**, **20** and **26**. Treatment of compound **18** with tetrabutylammonium fluoride in THF to remove the *tert*-butyldimethylsilyl group gave **21**, which was converted to **23** using hydrogenolysis reaction. In order to enhance the ability to diffuse across plasma membrane, the hydroxyl groups of compound **11** were protected with butyryl to synthesize **12**. Compounds **14**, **17** and **21** were further phosphorylated to provide **28–35** (Scheme 6).

Cytotoxicity evaluation

Non-small cell lung cancer (NSCLC) constitutes over 85% of primary lung cancers.[19] Although the treatment of advanced lung cancer is improving, survival of advanced NSCLC patients has been greatly limited by standard methods such as chemotherapy and radiotherapy.[20] The 5-year survival rate of NSCLC is still lacking in significant improvement. The major chemotherapy agents towards NSCLC are still cisplatin or its derivatives combined with other agents, which have apparent side effects in clinical therapies. For that matter, there is an urgent need to develop novel antitumor agents which can be successfully administered to NSCLC patients. Therefore, having established the synthesis of inositol phosphotriester analogues **9–27**, we assayed the inhibitory effects of these compounds against NSCLC cell line A549 firstly by the MTT test with cisplatin as positive control. The NSCLC cells were exposed to all the nineteen analogues at 10 μg mL^{-1} (final concentration in the test well). A compound was considered active if it reduced the growth of the cell line to 60% or less. The biological activity assay showed that analogues **14**, **16**, **17** and **21** were generally proved to be more potent than others. Analogues **11**, **15**, **20**, **26**, which were more similar to phosphatidylinositol in structure, exhibited little inhibition activity. The similar results were obtained with



Scheme 6 Synthesis of further phosphorylated analogues **28–35**. Reagents and conditions: (a) 1*H*-tetrazole, i-$Pr_2NP(OC_{10}H_{21})_2$ (**8**), CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 55% for **28**, 39% for **29**; (b) 1*H*-tetrazole, i-$Pr_2NP(OCH_3)_2$, CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 76% for **30**, 80% for **31**, 80% for **33**; (c) 1*H*-tetrazole, i-$Pr_2NP(OBn)_2$, CH_2Cl_2, RT, overnight, then *m*-CPBA, 0 °C–RT, 2 h, 70% for **32**, 70% for **35**; (d) Pd/C, ethanol, RT, overnight, 99% for **34**.

analogues **9**, **13**, **18**, **24**, which did not contain free hydroxyl groups. On the other hand, the inhibition activity was related with the phosphorylated position, 2-phosphorylated and 4(6)-phosphorylated analogues represented better inhibition activity. Analogues **14**, **16**, **17** and **21** were further tested in an eight-dose mode to determine their potency. Their IC_{50} values were in the 10–25 μM range (Table 1).

The natural phosphatidylinositol phosphates contain one more phosphate group at least to interact with the target. The hydroxyl groups of **14**, **17** and **21** were further converted to different phosphotriester groups to improve the biological activity (Scheme 6). Compounds **28** and **29**, which contain didecyl phosphates, showed little inhibition activity. Similar results were obtained with analogues **32** and **35**, which contain dibenzyl phosphates. The analogues containing dimethyl phosphates still exhibited antitumor activity, the IC_{50} values of **30** and **31** were equivalent to **17** and **21**. Moreover, the IC_{50} value of **33** advanced to 6.6 μM after phosphorylation of compound **14**, comparable to cisplatin. Removal of benzyl groups of **33** by catalytic hydrogenation to generate **34**, showed much less inhibition activity.

Table 1 Growth inhibition effects of inositol phosphotriester analogues on cancer cell lines and normal breast epithelial cell line MCF10A

	IC_{50} (μM)[a]				
Compound	A549	HepG2	MDA-MB-231	HeLa	MCF10A
14	16.6 ± 0.2	13.4 ± 0.6	22.2 ± 2.5	28.4 ± 1.0	>40.0
16	22.8 ± 2.0	13.7 ± 1.2	33.1 ± 0.2	23.6 ± 3.3	37.4 ± 1.7
17	14.0 ± 1.0	10.3 ± 0.5	15.2 ± 2.4	18.2 ± 2.5	29.6 ± 1.4
21	12.3 ± 0.6	10.6 ± 0.6	12.2 ± 1.9	16.1 ± 0.6	37.8 ± 1.1
30	16.4 ± 1.0	12.0 ± 1.2	16.3 ± 1.4	18.2 ± 2.5	>40.0
31	11.9 ± 1.5	8.5 ± 0.1	21.9 ± 2.4	15.4 ± 0.1	34.9 ± 0.8
33	6.6 ± 0.1	5.8 ± 0.2	6.2 ± 0.2	5.9 ± 0.2	15.0 ± 1.5
Cisplatin	7.0 ± 2.7	1.0 ± 0.1	8.0 ± 3.0	1.7 ± 0.1	3.4 ± 0.2

[a] IC_{50} values are the half-maximal inhibitory concentrations as measured by MTT assay; data represent the mean value ± SD. See the Experimental section for details.

The seven inositol phosphotriester analogues, which showed the highest potency against A549, were then screened for their anti-cancer activity against the other three human cancer cell lines (HepG2, MDA-MB-231 and HeLa) in order to determine the selectivity between different cancer cell lines (Table 1). Compound **14** exhibited better activities against HepG2 and A549 than MDA-MB-231 and HeLa. The cytotoxic activity of analogues **16** and **31** were higher against HepG2 than those against the other three cancer cell lines. Compounds **17**, **21**, **30** and **33** showed similar inhibition activities against all the four cancer cell lines. The general toxicity of these compounds was examined on the non-cancerous cell line MCF10A, and found to be less toxic than cisplatin (Table 1).

As initial research on the mechanism, these inositol phosphotriester analogues were tested for the ability to inhibit p100/p85 PI3K using the method of competitive fluorescence polarization,[21] but the inhibition activity was little. Actually, the biological result was unexpected and surprised for us. Analogues **11**, **15**, **20**, **26**, which were more similar to phosphatidylinositol, exhibited little inhibition activity. But some analogues phosphorylated at 2- or 4(6)-position, which contain benzyl groups and/or rigid structure, showed good antitumor activity. In addition, the active compounds **14**, **16**, **21**, **31** and **33** retained at least one benzyl group, which could be unlikely to be removed *in vitro*.[15a] But the benzyl groups were very important for the antitumor activity, especially analogues **14**, **21** and **33**. Also, the Falasca group has demonstrated that 2-*O*-Bn-Ins(1,3,4,5,6)P_5 exhibits enhanced antitumor activity.[12] Furthermore, the effect of 2-*O*-Bn-Ins(1,3,4,5,6)P_5 was highly specific, as this compound only inhibited PDK1 and to a lesser extent mTOR in a panel of almost 60 kinases.[12] However, the role of the benzyl group was still not clear. Examination of the X-ray crystal structure of the PH-domain of AKT, which binds to PtdIns(3,4,5)P_3 and PtdIns(3,4)P_2, indicates that benzyl groups could not be tolerated in the binding site, making it unlikely that these phosphotriester analogues are acting as inhibitors of the AKT PH-domain.[22] And, it could be difficult for these analogues to interact with a highly charged phosphate-binding domain. Maybe an alternative antitumor mechanism underlying cellular response to these agents exists. Our further work will focus on researching the mechanism. This will be useful for deep understanding of the signal transduction mechanism regulated by inositol phosphates and anticancer drugs design based on inositol phosphates.

Conclusion

In this paper, we report the synthesis and biological activity of several novel inositol phosphotriester analogues based on phosphatidylinositol. Seven compounds exhibited good cytotoxic activity against human cancer cell lines A549, HepG2, MDA-MB-231 and HeLa, especially compound **33** was cytotoxic against all the four cancer cell lines with good IC_{50} values. Moreover, the IC_{50} values of **33** against A549 and MDA-MB-231 were comparable to cisplatin. Further target study of these analogues is being actively pursued to elucidate the molecular basis of the drug–target interaction. To the best of our knowledge, this work represents the first attempt to examine the effects of inositol phosphotriester analogues on cancer cell growth inhibition properties.

Experimental section

Synthesis

General experimental procedures. Unless stated otherwise, commercial reagents and solvents were used without further purification. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (GF254) using UV light as the visualizing agent and phosphomolybdic acid and heat as developing agents. Column chromatography was performed on silica gel. All yields refer to isolated products. Melting points (mp) were determined on a TaiKe X-4 melting point apparatus and were uncorrected. ^{1}H NMR, ^{13}C NMR and ^{13}P NMR spectra were recorded on either 300 MHz or 400 MHz spectrometer. ^{1}H NMR chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ 0.00 ppm) or residual $CHCl_3$ (δ 7.26 ppm) in $CDCl_3$, ^{13}C NMR chemical shifts were reported using the central line of $CDCl_3$ (δ 77.0 ppm) as the internal standard. In other solvents, the solvent itself was used as the reference. High resolution mass spectral analyses (HRMS) were measured using ESI or MALDI ionization.

***meso*-D-*myo*-Inositol-1,3,5-*O*-orthoformate (1).** A solution of *myo*-inositol (18.0 g, 100 mmol) and triethyl orthoformate (30 mL) in anhydrous dimethyl formamide (180 mL) in the presence of *p*-toluenesulfonic acid monohydrate (5.2 g) was heated for 28 h at 110 °C under N_2. After cooling, saturated aqueous $NaHCO_3$ solution (25 mL) was added, and stirring was continued for 30 min. The color of the solution changed from dark brown to purple. The reaction mixture was evaporated to dryness *in vacuo*. The resulting syrup was recrystallized from hot methanol to yield **1** as a white solid (15.83 g, 83%): R_f 0.70 (dichloromethane–methanol 6 : 1); mp: 285 °C (dec); ^{1}H NMR (300 MHz, D_2O): δ_H = 4.27–4.31 (m, 3 H), 4.36 (m, 1 H), 4.62–4.64 (m, 2 H), 5.65 (s, 1 H); ^{13}C NMR (100.6 MHz, D_2O): δ_C = 59.6, 66.7, 69.3, 73.8, 102.1; HRMS *m*/*z* $[M - H]^-$ calcd for $C_7H_9O_6$ 189.0405, found 189.0407.

(±)-6-*O*-Benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate (2). Sodium hydride (60.5% dispersion; 1.59 g, 40 mmol) was added in batches to a stirred solution of *myo*-inositol orthoformate **1** (7.6 g, 40 mmol) and imidazole (100 mg) in anhydrous dimethyl formamide (150 mL) under N_2. The solution was stirred for 30 min, and then benzyl bromide (4.72 mL, 40 mmol) in anhydrous dimethyl formamide (10 mL) was added dropwise. After stirring overnight, the reaction was quenched with water and the solvent evaporated *in vacuo*. The residue dissolved in dichloromethane and water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 3), yielded **2** as a white solid (7.58 g, 68%): R_f 0.30 (ethyl acetate–petroleum ether 1 : 2); mp: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 3.18 (d, J = 12.0 Hz, 1 H), 3.75 (d, J = 10.0 Hz, 1 H), 4.09 (d, J = 11.6 Hz, 1 H), 4.21 (m, 1 H), 4.25 (m, 1 H), 4.29 (m, 1 H), 4.43–4.48 (m, 2 H), 4.67 (dd, J = 11.6, 16.8 Hz, 2 H), 5.44 (s, 1 H), 7.30–7.41 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 60.5, 67.2, 67.8, 72.1, 73.0, 74.1, 74.6, 102.6, 128.0, 128.7, 128.8, 135.8; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{16}O_6Na$ 303.0839, found 303.0837.

***meso*-2,4,6-Tri-*O*-benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate (3).** Sodium hydride (60.5% dispersion; 2.54 g, 64 mmol) was added in batches to a stirred solution of *myo*-inositol orthoformate **1** (3.45 g, 16 mmol) in anhydrous dimethyl formamide (70 mL) under N_2. The solution was stirred for 30 min, and then benzyl bromide (8.5 mL, 72 mmol) in anhydrous dimethyl formamide (10 mL) was added. After stirring overnight, the reaction was quenched with water and the solvent evaporated *in vacuo*. The residue dissolved in dichloromethane and water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 8), yielded **3** as a white solid (5.4 g, 74%): R_f 0.50 (ethyl acetate–petroleum ether 1 : 5); mp: 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.06 (m, 1 H), 4.30–4.32 (m, 2 H), 4.35 (t, J = 4.8 Hz, 2 H), 4.45 (m, 1 H), 4.55 (dd, J = 15.6, 72.0 Hz, 4 H), 4.65 (s, 2 H), 5.55 (s, 1 H), 7.21–7.40 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 67.1, 68.0, 70.4, 71.3, 71.4, 74.0, 103.1, 127.4, 127.6, 127.9, 128.2, 128.3, 137.5, 137.7; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{28}O_6Na$ 483.1778, found 483.1770.

***meso*-4,6-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate (4).** Sodium hydride (60.5% dispersion; 1.63 g, 40 mmol) was added in batches to a stirred solution of *myo*-inositol orthoformate **1** (3.8 g, 20 mmol) and imidazole (40 mg) in anhydrous dimethyl formamide (90 mL) under N_2. The solution was stirred for 30 min, and then benzyl bromide (5.8 mL, 48 mmol) in anhydrous dimethyl formamide (10 mL) was added dropwise. After stirring overnight, the reaction was quenched with water and the solvent evaporated *in vacuo*. The residue dissolved in dichloromethane and water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 3), yielded **4** as a colorless solid (3.56 g, 48%): R_f 0.20 (ethyl acetate–petroleum ether 1 : 3); mp: 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.12–4.17 (m, 3 H), 4.29–4.31 (m, 2 H), 4.39 (m, 1 H), 4.55 (dd, J = 11.7, 13.5 Hz, 4 H), 5.40 (s, 1 H), 7.18–7.24 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 61.4, 67.8, 71.7, 73.0, 73.8, 103.4, 127.7, 127.9, 128.5, 137.5; HRMS m/z [M + Na]$^+$ calcd for $C_{21}H_{22}O_6Na$ 393.1309, found 393.1303.

(±)-2-*O*-*tert*-Butyldimethylsilyl-6-*O*-benzyl-*myo*-inositol-1,3,5-*O*-orthoformate (5). Imidazole (4.62 g, 32.4 mmol) was added to a stirred solution of **2** (7.6 g, 27 mmol) in anhydrous dimethyl formamide (150 mL) under N_2. Then *tert*-butyldimethylsilyl chloride (4.9 mL, 67.5 mmol) in anhydrous dimethyl formamide (20 mL) was added dropwise under ice-water bath. After stirring overnight at room temperature, the reaction was quenched with water and the solvent evaporated *in vacuo*. The residue dissolved in dichloromethane and water. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 5), yielded **5** as a colorless oil (9.58 g, 90%): R_f 0.60 (ethyl acetate–petroleum ether 1 : 3); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 0.15 (s, 6 H), 0.95 (s, 9 H), 3.65 (d, J = 10.2 Hz, 1 H), 4.13–4.15 (m, 2 H), 4.26–4.27 (m, 2 H), 4.40–4.45 (m, 2 H), 4.66 (s, 2 H), 5.49 (s, 1 H), 7.26–7.40 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = −4.8, −4.7, 25.8, 60.8, 67.4, 68.2, 72.4, 73.0, 74.7, 74.8, 102.4, 127.9, 128.6, 128.8, 135.9; HRMS m/z [M + Na]$^+$ calcd for $C_{20}H_{30}O_6SiNa$ 417.1704, found 417.1705.

(±)-2,4,6-Tri-*O*-benzyl-3,5-*O*-ethylidene-D-*myo*-inositol (6). $AlMe_3$ (15 mL) in dry CH_2Cl_2 (10 mL) dropwise was added to a stirred solution of **3** (5.4g, 11.8 mmol) in dry CH_2Cl_2 (60 mL) under N_2 at 0 °C. The mixture was warmed to room temperature, stirred for 5 h, then poured into a solution of sodium potassium tartrate (150 g) in water (300 mL) and saturated aqueous ammonium chloride (300 mL), and stirred for 1 h at room temperature. The product was extracted into CH_2Cl_2, the combined organic layers were dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 9), yielded **6** as a colorless oil (3.8 g, 68%): R_f 0.20 (ethyl acetate–petroleum 1 : 8); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.23 (d, J = 4.8 Hz, 3 H), 3.21 (d, J = 6.6 Hz, 1 H), 3.81 (d, J = 6.2 Hz, 1 H), 3.97 (t, J = 3.7 Hz, 1 H), 4.15 (m, 1 H), 4.33 (m, 1 H), 4.39–4.44 (m, 3 H), 4.50 (d, J = 11.0 Hz, 1 H), 4.69 (d, J = 11.0 Hz, 1 H), 4.74–4.82 (m, 3 H), 5.26 (q, J = 4.9 Hz, 1 H), 7.25–7.39 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 20.9, 68.3, 68.8, 71.1, 71.8, 71.9, 72.5, 72.7, 73.0, 82.3, 90.7, 127.4, 127.5, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 137.2, 137.6, 138.4; HRMS m/z [M + Na]$^+$ calcd for $C_{29}H_{32}O_6Na$ 499.2091, found 499.2086.

(±)-2,4,6-Tri-*O*-benzyl-1,3-*O*-methylidene-D-*myo*-inositol (7). DIBAL (36 mL) in dry CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of **3** (8.2 g, 17.8 mmol) in dry CH_2Cl_2 (75 mL) under N_2 at 0 °C. The mixture was warmed to room temperature, stirred for 4 h, then poured into a solution of sodium potassium tartrate (108 g) in water (180 mL) and saturated aqueous ammonium chloride (144 mL), added ethyl acetate (430 mL), and stirred for 1 h at room temperature. The product was extracted into ethyl acetate, the combined organic layers were dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 4), yielded **7** as a colorless oil (7.6 g, 92%): R_f 0.25 (ethyl acetate–petroleum 1 : 4); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 4.08 (m, 1 H), 4.12–4.14 (m, 2 H), 4.41 (m, 1 H), 4.54–4.56 (m, 2 H), 4.63–4.77 (m, 7 H), 5.66 (d, J = 3.6 Hz, 1 H), 7.37–7.42 (m, 15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 69.5, 70.2, 70.8, 72.1, 72.7, 81.3, 85.7, 127.6, 127.8, 127.9, 128.0, 128.5, 128.6, 137.7, 138.0; HRMS m/z [M + Na]$^+$ calcd for $C_{28}H_{30}O_6Na$ 485.1935, found 485.1936.

Didecyl *N*,*N*-diisopropylphosphoramidite (8). Dry diisopropylamine (57 mL, 405.5 mmol) was added dropwise to a solution of phosphorus trichloride (17 mL, 194.8 mmol) in dry THF (200 mL) within one hour whilst stirring under N_2 in ice-salt bath. The resulting mixture was stirred at room temperature for three hours more, then filtered. The precipitate was washed with dry THF. After evaporation of THF, the yellow oil was distilled under reduced pressure to give *N*,*N*-diisopropylphosphoramide dichloridite (28.3 g, 71%): ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = 169.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.21 (d, J = 6.8 Hz, 12 H), 3.84–3.89 (m, 2 H).

Dry decanol (39 mL, 204.2 mmol) was added dropwise to a solution of *N*,*N*-diisopropylphosphoramide dichloridite (20.9 g, 101.4 mmol) and dry triethylamine (30 mL, 207.4 mmol) in dry THF (100 mL), within one hour whilst stirring under N_2 in ice-water bath. The resulting white slurry was stirred at room temperature for three hours more, and then filtered. The precipitate was washed with dry THF. After evaporation of THF, **8** was obtained as a colorless oil (36.9 g, 99%): ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = 145.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86 (t, J = 7.2 Hz, 6 H), 1.15 (d, J = 6.8 Hz, 12 H), 1.24 (s, 28 H), 1.55–1.62 (m, 4 H), 3.51–3.64 (m, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.6, 24.5, 24.6, 25.9, 29.31, 29.35, 29.5, 29.6, 31.26, 31.33, 31.9, 42.6, 42.7, 63.3, 63.5; HRMS m/z [M + H]$^+$ calcd for $C_{26}H_{57}NO_2P$ 446.4121, found 446.4125.

(±)-2,4,6-Tri-*O*-benzyl-3,5-*O*-ethylidene-D-*myo*-inositol-1-(didecyl phosphate) (9). Didecyl *N*,*N*-diisopropylphosphoramidite (1.16 g, 2.6 mmol) was stirred with 1*H*-tetrazole (182 mg, 2.6 mmol) in dry CH_2Cl_2 (25 mL) under N_2 for 30 min at room temperature. Compound **6** (612 mg, 1.3 mmol) dissolved in dry CH_2Cl_2 (25 mL) was added and the resulting mixture was stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (650 mg, 2.6 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 10, then 1 : 8), yielded **9** as a colorless oil (780 mg, 72%): R_f 0.30 (ethyl acetate–petroleum 1 : 8); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86–0.90 (m, 6 H), 1.19–1.23 (m, 31 H), 1.49–1.53 (m, 4 H), 3.88–4.00 (m, 5 H), 4.03 (m, 1 H), 4.30 (m, 1 H), 4.38–4.41 (m, 2 H), 4.48 (m, 1 H), 4.58 (m, 1 H), 4.65–4.69 (m, 2 H), 4.72–4.77 (m, 2 H), 5.17 (m, 1 H), 5.32 (m, 1 H), 7.28–7.37 (m, 15 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 20.6, 22.5, 25.18, 25.22, 29.0, 29.2, 29.4, 30.0, 30.08, 30.14, 31.7, 67.57, 67.63, 67.7, 68.5, 71.3, 71.7, 72.9, 73.0, 74.7, 74.8, 79.47, 79.55, 90.8, 127.36, 127.44, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 137.3, 137.9, 138.0; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{49}H_{73}O_9PNa$ 859.4885, found 859.4889.

(±)-2,4,6-Tri-*O*-benzyl-D-*myo*-inositol-1-(didecyl phosphate) (10). Concentrated hydrochloric acid (0.3 mL) was added to a stirred solution of **9** (360 mg, 0.43 mmol) in methanol (25 mL). The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 6, then 1 : 3), yielded **10** as a colorless oil (350 mg, 99%): R_f 0.20 (ethyl acetate–petroleum ether 1 : 3); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.23–1.25 (m, 28 H), 1.56–1.64 (m, 4 H), 3.52–3.58 (m, 2 H), 3.68 (m, 1 H), 3.89 (m, 1 H), 3.94–4.06 (m, 4 H), 4.26–4.31 (m, 2 H), 4.73–4.83 (m, 3 H), 4.87–4.92 (m, 3 H), 7.28–7.39 (m, 15 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.5, 25.2, 25.3, 29.0, 29.1, 29.4, 29.5, 30.1, 31.7, 67.9, 68.0, 71.6, 74.6, 74.7, 75.1, 75.3, 78.18, 79.22, 80.0, 81.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.9, 128.16, 128.19, 128.3, 138.4, 138.5, 138.6; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{47}H_{71}O_9PNa$ 833.4728, found 833.4732.

(±)-D-*myo*-Inositol-1-(didecyl phosphate) (11). 5% palladium black (300 mg) was added to a stirred solution of **10** (290 mg, 0.36 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **11** as a white solid (180 mg, 93%): mp: 187–189 °C; ^{31}P NMR (162 MHz, CD_3OD): δ_P = −1.7; ^{1}H NMR (400 MHz, CD_3OD): δ_H = 0.89 (t, *J* = 6.4 Hz, 6 H), 1.29 (m, 28 H), 1.67–1.69 (m, 4 H), 3.17 (t, *J* = 9.6 Hz, 1 H), 3.35 (d, *J* = 9.6 Hz, 1 H), 3.64 (t, *J* = 9.6 Hz, 1 H), 3.78 (t, *J* = 9.6 Hz, 1 H), 4.05–4.14 (m, 6 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ_C = 14.5, 23.8, 26.6, 30.3, 30.5, 30.7, 31.3, 31.4, 33.1, 69.3, 69.4, 69.5, 69.6, 72.5, 72.6, 72.8, 72.9, 73.9, 76.2, 80.6, 80.7; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{53}O_9PNa$ 563.3319, found 563.3325.

(±)-2,3,4,5,6-Penta-*O*-butyryl-D-*myo*-inositol-1-(didecyl phosphate) (12). Compound **11** (83 mg, 0.15 mmol) was dissolved in dry pyridine (6 mL), to the stirred solution was added DMAP (18 mg, 0.15 mmol) and butyric anhydride (0.26 mL, 1.5 mmol). After stirring overnight at room temperature, the reaction was quenched with water. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with dilute hydrochloric acid and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 6, then 1 : 4), yielded **12** as a colorless oil (120 mg, 90%): R_f 0.30 (ethyl acetate–petroleum ether 1 : 4); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.86–1.02 (m, 21 H), 1.25–1.32 (m, 28 H), 1.53–1.63 (m, 10 H), 1.66–1.74 (m, 4 H), 2.16–2.22 (m, 6 H), 2.26–2.35 (m, 2 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 3.91–3.99 (m, 4 H), 4.58 (ddd, *J* = 3.2, 10.0, 12.4 Hz, 1 H), 5.02 (dd, *J* = 2.4 Hz, 10.4 Hz, 1 H), 5.17 (t, *J* = 9.6 Hz, 1 H), 5.50 (dd, *J* = 9.6, 18.8 Hz, 2 H), 5.73 (t, *J* = 2.8 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 13.4, 13.50, 13.55, 14.0, 17.9, 18.0, 18.1, 18.2, 18.5, 22.6, 25.2, 25.3, 29.0, 29.2, 29.4, 30.0, 30.1, 31.8, 35.6, 35.76, 35.79, 35.9, 68.1, 68.2, 68.4, 68.5, 68.6, 68.9, 69.80, 69.85, 70.2, 72.78, 72.83, 171.9, 172.0, 172.1, 172.3; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{46}H_{83}O_{14}PNa$ 913.5413, found 913.5410.

***meso*-4,6-Di-*O*-benzyl-1,3,5-*O*-orthoformate-D-*myo*-inositol-2-(didecyl phosphate) (13).** Didecyl *N*,*N*-diisopropylphosphoramidite (900 mg, 2 mmol) was stirred with 1*H*-tetrazole (140 mg, 2 mmol) in dry CH_2Cl_2 (40 mL) under N_2 for 30 min at room temperature. Compound **4** (370 mg, 1 mmol) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (495 mg, 2 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 10, then 1 : 6), yielded **13** as a colorless oil (685 mg, 93%): R_f 0.20 (ethyl acetate–petroleum 1 : 6); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 7.0 Hz, 6 H), 1.25–1.33 (m, 28 H), 1.64–1.68 (m, 4 H), 4.05–4.09 (m, 4 H), 4.36–4.37 (m, 2 H), 4.44–4.46 (m, 3 H), 4.58–4.65 (m, 4 H), 4.95 (d, *J* = 7.2 Hz, 1 H), 5.50 (s, 1 H), 7.26–7.27 (m, 10 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 13.8, 22.4, 25.1, 28.8, 29.0, 29.2, 29.3, 29.9, 30.0, 31.6, 66.9, 67.0, 67.6, 67.8, 67.9, 70.7, 70.8, 71.2, 73.5, 102.9, 127.46, 127.55, 128.1, 137.1; HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{63}O_9PNa$ 753.4102, found 753.4098.

***meso*-4,6-Di-*O*-benzyl-D-*myo*-inositol-2-(didecyl phosphate) (14).** Concentrated hydrochloric acid (0.12 mL) was added to a stirred solution of **13** (110 mg, 0.15 mmol) in methanol (12 mL). The reaction mixture was stirred at room temperature for 1 h, and then heated to 35 °C for 6 h, concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 2, then 1 : 1), yielded **14** as a colorless oil (75 mg, 75%): R_f 0.20 (ethyl acetate–petroleum ether 1 : 1); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = 0.9; ^{1}H NMR(400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.0 Hz, 6 H), 1.26–1.37 (m, 28 H), 1.65–1.72 (m, 4 H), 2.62 (m, 1 H), 3.28–3.35 (m, 2 H), 3.56–3.62 (m, 4 H), 3.91 (s, 1 H), 4.05–4.13 (m, 4 H), 4.76 (d, *J* = 7.2 Hz, 1 H), 4.88 (dd, *J* =

11.2, 14.8 Hz, 4 H), 7.29–7.39 (m, 10 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.7, 25.5, 29.2, 29.3, 29.6, 30.2, 30.3, 31.9, 68.66, 68.72, 70.92, 70.95, 74.7, 75.0, 80.0, 80.11, 81.14, 127.9, 128.1, 128.5, 138.6; HRMS *m/z* [M + Na]$^+$ calcd for $C_{40}H_{65}O_9PNa$ 743.4258, found 743.4263.

***meso*-D-*myo*-Inositol-2-(didecyl phosphate) (15).** 5% palladium black (200 mg) was added to a stirred solution of **14** (75 mg, 0.1 mmol) in ethanol (10 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **15** as a white solid (42 mg, 80%): mp: 188–190 °C; ^{31}P NMR (162 MHz, CD_3OD): δ_P = −1.5; ^{1}H NMR (400 MHz, CD_3OD): δ_H = 0.91 (t, *J* = 6.4 Hz, 6 H), 1.32–1.42 (m, 28 H), 1.67–1.71 (m, 4 H), 3.22 (t, *J* = 8.8 Hz, 1 H), 3.50–3.60 (m, 4 H), 4.14–4.19 (m, 4 H), 4.71 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ_C = 14.5, 23.8, 26.7, 30.4, 30.5, 30.76, 30.79, 31.37, 31.44, 33.1, 69.47, 69.54, 71.80, 71.83, 74.3, 76.4, 82.8, 82.9; HRMS *m/z* [M + Na]$^+$ calcd for $C_{26}H_{53}O_9PNa$ 563.3319, found 563.3310.

(±)-4-*O*-Benzyl-1,3,5-*O*-orthoformate-D-*myo*-inositol-2-(didecyl phosphate) (16). 5% palladium black (150 mg) was added to a stirred solution of **13** (100 mg, 0.13 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 4), yielded **16** as a colorless oil (20 mg, 24%): R_f 0.20 (ethyl acetate–petroleum 1 : 4); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, *J* = 6.8 Hz, 6 H), 1.25–1.38 (m, 28 H), 1.68–1.71 (m, 4 H), 4.06–4.12 (m, 4 H), 4.26 (m, 1 H), 4.36 (m, 1 H), 4.41 (m, 1 H), 4.47 (m, 1 H), 4.53 (m, 1 H), 4.68 (dd, *J* = 11.6, 52.4 Hz, 2 H), 4.84 (m, 1 H), 5.47 (s, 1 H), 7.32–7.40 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.6, 25.4, 29.1, 29.3, 29.5, 29.7, 30.15, 30.17, 30.21, 30.24, 31.8, 66.37, 66.41, 67.5, 68.1, 68.27, 68.33, 70.27, 70.30, 72.8, 72.97, 73.02, 73.9, 102.5, 128.3, 128.8, 128.9, 135.6; HRMS *m/z* [M + Na]$^+$ calcd for $C_{34}H_{57}O_9PNa$ 663.3632, found 663.3630.

***meso*-1,3,5-*O*-Orthoformate-D-*myo*-inositol-2-(didecyl phosphate) (17).** 5% palladium black (350 mg) was added to a stirred solution of **13** (157 mg, 0.2 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **17** as a colorless oil (110 mg, 99%): R_f 0.20 (ethyl acetate–petroleum 1 : 2); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 7.2 Hz, 6 H), 1.26–1.39 (m, 28 H), 1.66–1.73 (m, 4 H), 4.06–4.11 (m, 4 H), 4.30 (m, 1 H), 4.36–4.40 (m, 2 H), 4.56–4.58 (m, 2 H), 4.89 (m, 1 H), 5.47 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.7, 25.4, 29.1, 29.3, 29.48, 29.52, 30.07, 30.14, 31.9, 67.2, 67.3, 67.9, 68.2, 68.7, 68.8, 72.8, 72.9, 102.4; HRMS *m/z* [M + Na]$^+$ calcd for $C_{27}H_{51}O_9PNa$ 573.3163, found 573.3160.

(±)-2-*O*-*tert*-Butyldimethylsilyl-6-*O*-benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate-4-(didecyl phosphate) (18). Didecyl *N*,*N*-diisopropylphosphoramidite (900 mg, 2 mmol) was stirred with 1*H*-tetrazole (140 mg, 2 mmol) in dry CH_2Cl_2 (40 mL) under N_2 for 30 min at room temperature. Compound **5** (403 mg, 1 mmol) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (504 mg, 2 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 15, then 1 : 10), yielded **18** as a colorless oil (450 mg, 60%): R_f 0.20 (ethyl acetate–petroleum 1 : 10); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.15 (s, 6 H), 0.88 (t, *J* = 6.8 Hz, 6 H), 0.94 (s, 9 H), 1.24–1.26 (m, 28 H), 1.52–1.63 (m, 4 H), 3.87–3.99 (m, 4 H), 4.15 (m, 1 H), 4.21 (m, 1 H), 4.30–4.33 (m, 2 H), 4.54–4.72 (m, 3 H), 5.07 (m, 1 H), 5.52 (s, 1 H), 7.28–7.35 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = −4.92, −4.88, 13.9, 18.2, 22.5, 25.17, 25.21, 25.7, 28.9, 29.1, 29.3, 29.9, 30.0, 30.1, 31.7, 60.8, 67.60, 67.64, 68.0, 68.09, 68.14, 70.87, 70.92, 71.4, 72.8, 73.7, 102.7, 127.1, 127.6, 128.2, 137.3; HRMS *m/z* [M + Na]$^+$ calcd for $C_{40}H_{71}O_9PSiNa$ 777.4497, found 777.4497.

(±)-6-*O*-Benzyl-D-*myo*-inositol-4-(didecyl phosphate) (19). Concentrated hydrochloric acid (0.16 mL) was added to a stirred solution of **18** (200 mg, 0.26 mmol) in methanol (15 mL). The reaction mixture was stirred at room temperature for 1 h, then heated to 40 °C for 6 h, concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 1, then 2 : 1), yielded **19** as a colorless oil (160 mg, 95%): R_f 0.30 (ethyl acetate–petroleum ether 2 : 1); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = 1.0; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 7.2 Hz, 6 H), 1.26–1.36 (m, 28 H), 1.65–1.72 (m, 4 H), 2.69 (m, 1 H), 3.25 (m, 1 H), 3.56–3.63 (m, 3 H), 3.72 (m, 1 H), 3.91 (s, 2 H), 4.09–4.17 (m, 4 H), 4.22 (m, 1 H), 4.44 (m, 1 H), 4.90 (dd, *J* = 11.2, 30.8 Hz, 2 H), 7.30–7.40 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.7, 25.4, 29.2, 29.3, 29.5, 30.1, 30.2, 31.9, 52.6, 68.6, 68.66, 68.71, 71.2, 71.8, 72.3, 73.62, 73.65, 75.1, 81.4, 81.66, 81.72, 127.8, 128.1, 128.5, 128.9, 131.1, 138.7; HRMS *m/z* [M + Na]$^+$ calcd for $C_{33}H_{59}O_9PNa$ 653.3789, found 653.3796.

(±)-D-*myo*-Inositol-4-(didecyl phosphate) (20). 5% palladium black (200 mg) was added to a stirred solution of **19** (100 mg, 0.16 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **20** as a white solid (60 mg, 82%): mp: 193–195 °C; ^{31}P NMR (162 MHz, CD_3OD): δ_P = −0.6; ^{1}H NMR (400 MHz, CD_3OD): δ_H = 0.85–0.91 (m, 6 H), 1.28–1.38 (m, 28 H), 1.60–1.72 (m, 4 H), 3.33–3.36 (m, 2 H), 3.52 (m, 1 H), 3.62 (m, 1 H), 3.94 (m, 1 H), 4.10–4.12 (m, 4 H), 4.37 (m, 1 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ_C = 14.5, 23.8, 26.7, 30.4, 30.5, 30.76, 30.78, 31.3, 31.4, 33.1, 69.36, 69.39, 69.42, 69.5, 72.28, 72.31, 73.1, 74.3, 75.0, 75.1, 83.3, 83.4; HRMS *m/z* $[M + Na]^+$ calcd for $C_{26}H_{53}O_9PNa$ 563.3319, found 563.3323.

(±)-6-*O*-Benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate-4-(didecyl phosphate) (21). TBAF (0.56 mL, 0.56 mmol) was added to compound **18** (280 mg, 0.37 mmol) in dry THF (20 mL), after the mixture was stirred for 30 min at room temperature, quenched with water. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 4), yielded **21** as a colorless oil (232 mg, 98%): R_f 0.20 (ethyl acetate–petroleum 1 : 4); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.24–1.26 (m, 28 H), 1.53–1.64 (m, 4 H), 3.90–4.01 (m, 4 H), 4.14 (m, 1 H), 4.23 (m, 1 H), 4.29 (m, 1 H), 4.36 (m, 1 H), 4.55–4.72 (m, 3 H), 5.10 (m, 1 H), 5.47 (s, 1 H), 7.31–7.34 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.3, 29.0, 29.2, 29.4, 30.0, 30.08, 30.14, 31.8, 60.5, 67.48, 67.52, 68.2, 68.29, 68.34, 70.45, 70.5, 71.54, 72.59, 72.65, 73.2, 103.0, 127.4, 127.8, 128.3, 137.2; HRMS *m/z* $[M + Na]^+$ calcd for $C_{34}H_{57}O_9PNa$ 663.3632, found 663.3635.

(±)-2-*O*-*tert*-Butyldimethylsilyl-D-*myo*-inositol-1,3,5-*O*-orthoformate-4-(didecyl phosphate) (22). 5% palladium black (300 mg) was added to a stirred solution of **18** (125 mg, 0.15 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **22** as a colorless oil (100 mg, 91%): R_f 0.20 (ethyl acetate–petroleum 1 : 5); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −2.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.15 (s, 6 H), 0.88 (t, *J* = 6.8 Hz, 6 H), 0.95 (s, 9 H), 1.26 (m, 28 H), 1.68–1.69 (m, 4 H), 4.05–4.10 (m, 4 H), 4.14 (m, 1 H), 4.19 (m, 1 H), 4.28 (m, 1 H), 4.52 (m, 1 H), 4.57 (m, 1 H), 5.03 (m, 1 H), 5.52 (s, 1 H); ^{13}C NMR(100.6 MHz, $CDCl_3$): δ_C = −4.8, −4.7, 14.0, 18.3, 22.6, 25.3, 25.8, 29.0, 29.2, 29.4, 30.1, 30.17, 30.24, 31.8, 60.46, 67.53, 68.8, 68.9, 68.95, 68.98, 72.08, 72.13, 72.77, 72.85, 74.3, 102.6; HRMS *m/z* $[M + Na]^+$ calcd for $C_{33}H_{65}O_9PSiNa$ 687.4028, found 687.4032.

(±)-D-*myo*-Inositol-1,3,5-*O*-orthoformate-4-(didecyl phosphate) (23). 5% palladium black (350 mg) was added to a stirred solution of **21** (130 mg, 0.2 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **23** as a colorless oil (100 mg, 91%): R_f 0.50 (ethyl acetate–petroleum 1 : 1); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −2.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.26 (m, 28 H), 1.66–1.72 (m, 4 H), 4.06–4.10 (m, 4 H), 4.14 (m, 1 H), 4.22 (m, 1 H), 4.28 (m, 1 H), 4.56 (m, 1 H), 4.60 (m, 1 H), 5.07 (m, 1 H), 5.47 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.3, 29.0, 29.2, 29.4, 29.6, 30.08, 30.15, 30.2, 31.8, 60.1, 67.1, 68.65, 68.68, 68.8, 68.88, 68.94, 71.5, 71.6, 72.36, 72.44, 74.0, 102.8; HRMS *m/z* $[M + Na]^+$ calcd for $C_{27}H_{51}O_9PNa$ 573.3163, found 573.3165.

***meso*-2,4,6-Tri-*O*-benzyl-1,3-*O*-methylidene-D-*myo*-inositol-5-(didecyl phosphate) (24).** Didecyl *N*,*N*-diisopropylphosphoramidite (360 mg, 0.75 mmol) was stirred with 1*H*-tetrazole (62 mg, 0.75 mmol) in dry CH_2Cl_2 (20 mL) under N_2 for 30 min at room temperature. Compound **7** (120 mg, 0.25 mmol) dissolved in dry CH_2Cl_2 (10 mL) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (190 mg, 0.75 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 15, 1 : 10, then 1 : 8), yielded **24** as a colorless oil (175 mg, 86%): R_f 0.20 (ethyl acetate–petroleum 1 : 8); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.24–1.29 (m, 28 H), 1.58–1.65 (m, 4 H), 3.93–4.02 (m, 4 H), 4.07–4.08 (m, 2 H), 4.17 (m, 1 H), 4.33–4.35 (m, 2 H), 4.60–4.74 (m, 8 H), 5.45 (d, *J* = 4.4 Hz, 1 H), 7.26–7.33 (m, 15 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.6, 25.4, 29.1, 29.3, 29.5, 30.1, 30.2, 31.8, 67.8, 67.9, 69.9, 70.6, 70.9, 71.8, 73.67, 73.74, 80.49, 80.53, 85.2, 127.5, 127.6, 127.8, 128.3, 128.4, 137.61, 137.65; HRMS *m/z* $[M + Na]^+$ calcd for $C_{48}H_{71}O_9PNa$ 845.4728, found 845.4732.

***meso*-2,4,6-Tri-*O*-benzyl-D-*myo*-inositol-5-(didecyl phosphate) (25).** Concentrated hydrochloric acid (0.5 mL) was added to a stirred solution of **24** (110 mg, 0.12 mmol) in methanol (15 mL). The reaction mixture was stirred at room temperature for 1 h, refluxed for 6 h, concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 2, then 2 : 3), yielded **25** as a colorless oil (82 mg, 80%): R_f 0.15 (ethyl acetate–petroleum ether 2 : 3); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, *J* = 6.8 Hz, 6 H), 1.18–1.29 (m, 28 H), 1.47–1.50 (m, 4 H), 2.50–2.52 (m, 2 H), 3.50–3.54 (m, 2 H), 3.76–3.80 (m, 2 H), 3.86–3.90 (m, 3 H), 3.95–3.99 (m, 2 H), 4.37 (m, 1 H), 4.79 (s, 2 H), 4.83 (dd, *J* = 11.2, 60.0 Hz, 4 H), 7.25–7.44 (m, 15 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.7, 25.4, 29.2, 29.3, 29.5, 30.2, 30.3, 31.9, 67.9, 68.0, 71.9, 74.5, 75.2, 79.2, 80.2, 80.3, 80.49, 80.52, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 138.5, 138.6; HRMS *m/z* $[M + Na]^+$ calcd for $C_{47}H_{71}O_9PNa$ 833.4728, found 833.4730.

***meso*-D-*myo*-Inositol-5-(didecyl phosphate) (26).** 5% palladium black (270 mg) was added to a stirred solution of **25** (70 mg, 0.09 mmol) in ethanol (10 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **26** as a white solid

(30 mg, 73%): mp: 206–208 °C; ^{31}P NMR (162 MHz, CD_3OD): δ_P = −1.3; ^{1}H NMR (400 MHz, CD_3OD): δ_H = 0.90 (t, J = 6.4 Hz, 6 H), 1.30–1.40 (m, 28 H), 1.65–1.70 (m, 4 H), 3.36–3.39 (m, 2 H), 3.73–3.78 (m, 2 H), 3.96–4.02 (m, 2 H), 4.11–4.16 (m, 4 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ_C = 14.5, 23.8, 26.7, 30.4, 30.5, 30.76, 30.78, 31.36, 31.43, 33.1, 69.37, 69.43, 73.0, 73.1, 73.2, 73.8, 84.46, 84.53; HRMS m/z [M + Na]$^+$ calcd for $C_{26}H_{53}O_9PNa$ 563.3319, found 563.3322.

***meso*-1,3-*O*-Methylidene-D-*myo*-inositol-5-(didecyl phosphate) (27).** 5% palladium black (450 mg) was added to a stirred solution of **24** (120 mg, 0.15 mmol) in ethanol (15 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 1, then 3 : 2), yielded **27** as a colorless oil (72 mg, 90%): R_f 0.20 (ethyl acetate–petroleum ether 3 : 2); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −0.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.8 Hz, 6 H), 1.25–1.34 (m, 28 H), 1.63–1.70 (m, 4 H), 2.80 (m, 1 H), 3.90 (s, 1 H), 4.04–4.09 (m, 5 H), 4.16–4.31 (m, 4 H), 4.62–4.72 (m, 2 H), 4.75 (d, J = 6.0 Hz, 1 H), 5.07 (d, J = 6.0 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.4, 29.1, 29.3, 29.5, 30.08, 30.15, 31.8, 52.6, 62.0, 65.5, 68.7, 68.8, 73.09, 73.14, 83.0, 83.1, 85.1; HRMS m/z [M + Na]$^+$ calcd for $C_{27}H_{53}O_9PNa$ 575.3319, found 575.3313.

(±)-1,3,5-*O*-Orthoformate-D-*myo*-inositol-2,4-bi(didecyl phosphate) (28) and *meso*-1,3,5-*O*-orthoformate-D-*myo*-inositol-2,4,6-tri(didecyl phosphate) (29). Didecyl *N*,*N*-diisopropylphosphoramidite (116 mg, 0.24 mmol) was stirred with 1*H*-tetrazole (19 mg, 0.24 mmol) in dry CH_2Cl_2 (5 mL) under N_2 for 30 min at room temperature. Compound **17** (33 mg, 0.06 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (64 mg, 0.24 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 6, 1 : 4, 1 : 3, then 1 : 2), yielded **28** as a colorless oil (30 mg, 55%): R_f 0.10 (ethyl acetate–petroleum 1 : 4); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −2.2, −1.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, J = 6.8 Hz, 12 H), 1.20–1.40 (m, 56 H), 1.68–1.70 (m, 8 H), 3.90 (m, 1 H), 4.08–4.09 (m, 8 H), 4.40 (m, 1 H), 4.46 (m, 1 H), 4.57–4.62 (m, 2 H), 4.87 (d, J = 3.2 Hz, 1 H), 5.06 (m, 1H), 5.50 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.6, 25.36, 25.38, 29.10, 29.13, 29.3, 29.5, 30.11, 30.14, 30.17, 30.21, 31.8, 65.9, 66.0, 67.1, 68.2, 68.3, 68.82, 68.83, 68.9, 69.0, 70.69, 70.74, 70.78, 70.82, 71.36, 71.41, 72.20, 72.24, 76.7, 102.6; HRMS m/z [M + Na]$^+$ calcd for $C_{47}H_{92}O_{12}P_2Na$ 933.5956, found 933.5945; yielded **29** as a colorless oil (30 mg, 39%): R_f 0.20 (ethyl acetate–petroleum 1 : 4); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7, −1.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.80–0.90 (m, 18 H), 1.20–1.40 (m, 84 H), 1.67–1.69 (m, 12 H), 4.07–4.08 (m, 12 H), 4.50–4.55 (m, 3 H), 4.79 (m, 1 H), 5.10–5.13 (m, 2 H), 5.51 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.1, 22.6, 25.38, 25.42, 29.1, 29.2, 29.3, 29.5, 30.2, 30.26, 30.33, 31.9, 65.30, 65.34, 67.9, 67.99, 68.04, 68.2, 68.3, 68.49, 68.55, 70.6, 70.69, 70.74, 102.6; HRMS m/z [M + Na]$^+$ calcd for $C_{67}H_{133}O_{15}P_3Na$ 1293.8749, found 1293.8752.

***meso*-1,3,5-*O*-Orthoformate-D-*myo*-inositol-4,6-bi(dimethyl phosphate)-2-(didecyl phosphate) (30).** Dimethyl *N*,*N*-diisopropylphosphoramidite (75 mg, 0.348 mmol) was stirred with 1*H*-tetrazole (24 mg, 0.348 mmol) in dry CH_2Cl_2 (5 mL) under N_2 for 30 min at room temperature. Compound **17** (48 mg, 0.087 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (88 mg, 0.348 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 1), then ethyl acetate and petroleum ether and methanol (1 : 1 : 0.06), yielded **30** as a colorless oil (51 mg, 76%): R_f 0.10 (ethyl acetate–petroleum–methanol 1 : 1 : 0.06); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.5, 0.1; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (t, J = 6.6 Hz, 6 H), 1.23–1.35 (m, 28 H), 1.64–1.71 (m, 4 H), 3.78 (s, 6 H), 3.81 (s, 6 H), 4.05–4.08 (m, 4 H), 4.46–4.50 (m, 2 H), 4.56 (m, 1 H), 4.78 (d, J = 3.6 Hz, 1 H), 5.10–5.12 (m, 2 H), 5.50 (s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.3, 29.1, 29.2, 29.43, 29.46, 30.08, 30.15, 31.8, 54.78, 54.83, 54.84, 65.12, 65.16, 67.70, 67.75, 67.8, 68.3, 68.4, 70.2, 70.3, 70.49, 70.53, 70.6, 102.5; HRMS m/z [M + Na]$^+$ calcd for $C_{31}H_{61}O_{15}P_3Na$ 789.3115, found 789.3113.

(±)-6-*O*-Benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate-2-(dimethyl phosphate)-4-(didecyl phosphate) (31). Dimethyl *N*,*N*-diisopropylphosphoramidite (46 mg, 0.2 mmol) was stirred with 1*H*-tetrazole (16 mg, 0.2 mmol) in dry CH_2Cl_2 (10 mL) under N_2 for 30 min at room temperature. Compound **21** (68 mg, 0.1 mmol) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (51 mg, 0.2 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 4, 1 : 3, then 1;2), yielded **31** as a colorless oil (60 mg, 80%): R_f 0.10 (ethyl acetate–petroleum 1 : 2); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.8, 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, J = 6.8 Hz, 6 H), 1.24–1.33 (m, 28 H), 1.54–1.65 (m, 4 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.89–4.02 (m, 4 H), 4.38 (m,1 H), 4.46–4.50 (m, 2 H), 4.58 (m, 1 H), 4.64 (dd, J = 11.6, 29.6 Hz, 2 H), 4.88 (d, J = 6.8 Hz, 1 H), 5.10 (m, 1 H), 5.51 (s, 1 H), 7.29–7.35 (m, 5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.31, 25.32, 29.1, 29.2, 29.43, 29.45, 30.06, 30.13, 30.2, 31.8, 54.5, 54.6, 66.60, 66.65, 67.64, 67.68, 68.3, 68.4, 68.5, 70.38, 70.43, 70.61, 70.65, 70.80, 70.84, 70.9, 71.6, 73.0, 102.8, 127.7, 128.0, 128.4, 136.9; HRMS m/z [M + Na]$^+$ calcd for $C_{36}H_{62}O_{12}P_2Na$ 771.3609, found 771.3612.

(±)-6-*O*-Benzyl-D-*myo*-inositol-1,3,5-*O*-orthoformate-2-(dibenzyl phosphate)-4-(didecyl phosphate) (32). Dibenzyl *N*,*N*-diisopropylphosphoramidite (82 mg, 0.2 mmol) was stirred with 1*H*-tetrazole (17 mg, 0.2 mmol) in dry CH_2Cl_2 (10 mL) under N_2 for 30 min at room temperature. Compound **21** (64 mg, 0.1 mmol) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (50 mg, 0.2 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 6, 1 : 4, then 1 : 3), yielded **32** as a colorless oil (63 mg, 70%): R_f 0.10 (ethyl acetate–petroleum 1 : 3); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.8, −1.7; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.88 (t, J = 6.8 Hz, 6 H), 1.22–1.30 (m, 28 H), 1.51–1.61 (m, 4 H), 3.83–3.98 (m, 4 H), 4.33 (m, 1 H), 4.38–4.42 (m, 2 H), 4.57 (m, 1 H), 4.58 (dd, J = 11.6, 27.6 Hz, 2 H), 4.90 (d, J = 3.2 Hz, 1 H), 5.08–5.11 (m, 5 H), 5.51 (s, 1 H), 7.28–7.33 (m, 15 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.3, 29.1, 29.2, 29.42, 29.45, 30.0, 30.1, 30.2, 31.8, 66.68, 66.73, 67.65, 67.68, 68.28, 68.34, 68.37, 68.43, 69.51, 69.54, 69.6, 70.38, 70.43, 70.5, 70.7, 70.8, 70.9, 71.5, 73.0, 102.8, 127.6, 127.90, 127.93, 128.4, 128.5, 135.41, 135.44, 135.49, 135.51, 136.9; HRMS m/z [M + Na]$^+$ calcd for $C_{48}H_{70}O_{12}P_2Na$ 923.4235, found 923.4230.

***meso*-4,6-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-tri(dimethyl phosphate)-2-(didecyl phosphate) (33).** Dimethyl *N*,*N*-diisopropylphosphoramidite (255 mg, 1.224 mmol) was stirred with 1*H*-tetrazole (87 mg, 1.224 mmol) in dry CH_2Cl_2 (10 mL) under N_2 for 30 min at room temperature. Compound **14** (98 mg, 0.136 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (335 mg, 1.224 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 1), then ethyl acetate and petroleum ether and methanol (1 : 1 : 0.15), yielded **33** as a colorless oil (140 mg, 99%): R_f 0.20 (ethyl acetate–petroleum–methanol 1 : 1 : 0.15); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7, 0.9, 1.1; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.8 Hz, 6 H), 1.20–1.41 (m, 28 H), 1.68–1.77 (m, 4 H), 3.45 (s, 3 H), 3.49 (s, 3 H), 3.59 (s, 3 H), 3.63 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.94 (t, J = 9.6 Hz, 2 H), 4.08–4.15 (m, 4 H), 4.38–4.51 (m, 3 H), 4.83 (s, 4 H), 5.13 (d, J = 0.9 Hz, 1 H), 7.21–7.45 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 13.9, 22.5, 25.4, 29.1, 29.2, 29.4, 30.1, 30.2, 31.7, 54.26, 54.34, 54.4, 54.5, 54.6, 68.1, 68.2, 74.7, 75.2, 76.7, 76.8, 77.7, 79.0, 79.1, 127.2, 127.9, 137.7; HRMS m/z [M + Na]$^+$ calcd for $C_{46}H_{80}O_{18}P_4Na$ 1067.4187, found 1067.4179.

***meso*-D-*myo*-Inositol-1,3,5-tri(dimethyl phosphate)-2-(didecyl phosphate) (34).** 5% palladium black (180 mg) was added to a stirred solution of **33** (65 mg, 0.06 mmol) in ethanol (10 mL), and the flask was flushed three times with a balloon of hydrogen. After the reaction mixture was stirred overnight at room temperature, the catalyst was removed by filtering through Celite. The combined organic layers were concentrated under reduced pressure, yielded **34** as a colorless oil (50 mg, 98%): R_f 0.20 (ethyl acetate–petroleum ether–methanol 1 : 1 : 0.2); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.9, 1.1, 1.6; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.4 Hz, 6 H), 1.22–1.38 (m, 28 H), 1.62–1.72 (m, 4 H), 3.83–3.88 (m, 18 H), 3.97–4.10 (m, 6 H), 4.49 (m, 1 H), 4.62 (t, J = 9.6 Hz, 2 H), 5.08 (d, J = 8.4 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C = 14.0, 22.6, 25.4, 29.1, 29.2, 29.5, 30.1, 30.2, 31.8, 54.7, 54.8, 54.96, 55.02, 55.04, 55.1, 68.0, 68.1, 70.8, 75.7, 81.4, 81.5; HRMS m/z [M + Na]$^+$ calcd for $C_{32}H_{68}O_{18}P_4Na$ 887.3248, found 887.3244.

***meso*-4,6-Di-*O*-benzyl-D-*myo*-inositol-1,3,5-tri(dibenzyl phosphate)-2-(didecyl phosphate) (35).** Dibenzyl *N*,*N*-diisopropylphosphoramidite (423 mg, 1.224 mmol) was stirred with 1*H*-tetrazole (86 mg, 1.224 mmol) in dry CH_2Cl_2 (10 mL) under N_2 for 30 min at room temperature. Compound **14** (98 mg, 0.136 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added and the resulting mixture stirred overnight. The mixture was cooled to 0 °C, and 3-chloroperoxybenzoic acid (346 mg, 1.224 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 2 h. The 3-chloroperoxybenzoic acid was quenched with a 10% aqueous solution of sodium hydrogen sulfite. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with ethyl acetate and petroleum ether (1 : 3, 1 : 2, then 1 : 1), yielded **35** as a colorless a colorless oil (186 mg, 91%): R_f 0.30 (ethyl acetate–petroleum 1 : 1); ^{31}P NMR (162 MHz, $CDCl_3$): δ_P = −1.7, −1.6, −1.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.87 (t, J = 6.8 Hz, 6 H), 1.22–1.32 (m, 28 H), 1.59–1.66 (m, 4 H), 3.99 (t, J = 9.6 Hz, 2 H), 4.05–4.13 (m, 4 H), 4.33–4.38 (m, 2 H), 4.46 (m, 1 H), 4.60–4.66 (m, 2 H), 4.77–4.89 (m, 8 H), 4.95–5.00 (m, 6 H), 5.29 (d, J = 7.2 Hz, 1 H), 6.96–6.98 (m, 4 H), 7.11–7.12 (m, 4 H), 7.16–7.26 (m, 28 H), 7.37–7.39 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C = 14.0, 22.5, 25.4, 29.14, 29.19, 29.5, 30.1, 30.2, 31.8, 68.2, 68.3, 69.16, 69.23, 69.26, 69.33, 69.5, 69.6, 74.6, 75.2, 75.3, 77.7, 127.2, 127.4, 127.6, 127.8, 128.0, 128.1, 128.2, 128.28, 128.33, 135.5, 135.56, 135.60, 135.64, 135.70, 135.73, 137.7; HRMS m/z $[M + Na]^+$ calcd for $C_{82}H_{104}O_{18}P_4Na$ 1523.6065, found 1523.6060.

Antiproliferative assay

Non-small cell lung cancer cell line A549, liver cancer cell line HepG2, breast cancer cell line MDA-MB-231, cervical carcinoma cell line HeLa and normal breast epithelial cell line MCF10A were obtained from ATCC (American type culture collection) and were maintained in 5% CO_2 at 37 °C. A549, HepG2, MDA-MB-231 and HeLa cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 10% fetal bovine serum (FBS, Omega Scientific) and 1% penicillin/streptomycin (Omega Scientific). MCF10A cells were grown in DMEM/F12 (Gibco) supplemented with 5% horse serum, 20 ng mL^{-1} EGF (Peprotech), 0.5 μg mL^{-1} hydrocortisone (Sigma), 100 ng mL^{-1} cholera toxin (Sigma), 10 μg mL^{-1} insulin (Sigma), 1% Pen/Strep (Invitrogen). Cisplatin (Sigma) was dissolved in 1% NaCl (Sigma) solution (pH 7).

Approximately 1000 cells were seeded into individual wells of 96-well tissue culture plates and incubated for 12 h, medium was 0.2 mL per well. The compound was diluted to 10 μg mL^{-1} using DMEM (final concentration in the test well), to analyze the inhibition effect on A549 roughly. After that, cells were exposed to triplicates of different concentration solutions (from 0.39 to 50 μg mL^{-1}) of test compounds to determine their potency. The analyzed inhibitors were dissolved in DMSO reaching a final DMSO concentration of 0.5%. Viability was normalized to control cells which were treated with the vehicle, DMSO. After 72 h incubation at 37 °C and 5% CO_2, cell viability was assessed by MTT assay. Cells were replenished with fresh medium (0.1 mL per well) which contains 10% MTT. Culture medium was removed after 4 h, and the formazan was dissolved in DMSO (200 μL per well). Then OD_{570} were measured by Plate Reader (BIORAD). The IC_{50} values were calculated by Origin 6.0.

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